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# ARCHIVES OF SURGERY

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JULY 1935

NUMBER 1

## EFFECT OF FUNDUSECTOMY ON THE ACIDITY OF THE GASTRIC AND DUODENAL CONTENT

AN EXPERIMENTAL STUDY

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Most surgical procedures for treatment of peptic ulcer are used in an endeavor to cause reduction in gastric acidity or in the length of time the ulcer is exposed to the gastric content. These results are brought about either by increasing the speed with which the stomach empties or by causing mixing of the alkaline duodenal sections with the gastric content through an altered or artificial stoma. In all probability few, if any, of the procedures employed affect directly the secretory mechanism involved in the production of hydrochloric acid. It would seem more logical in uncomplicated cases to perform some procedure which would reduce the ability of the stomach to produce hydrochloric acid. With this hypothesis in view experimental work was carried out on dogs in an effort to determine what effect removal of varying portions of acid-secreting mucous membrane has on the acidity of the gastric and duodenal content.

Anatomically the important structures of the stomach intimately concerned with secretion of gastric juice are the nerves and the glands. The innervation is through the vagus and the sympathetic nerves, but, as has been shown by Pavlov,<sup>1</sup> the vagus nerves contain the fibers which are important in the initiation of secretion of acid. The action of the sympathetic fibers is not so well understood, although the recent work of Baxter<sup>2</sup> indicates that the fibers are concerned with the production of alkaline mucus.

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\* Formerly Fellow in Surgery, the Mayo Foundation, Rochester, Minn.

An abridgment of a thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Surgery.

1. Pavlov, I. P.: *The Work of the Digestive Glands*, London, C. Griffin & Company, Ltd., 1910.

2. Baxter, S. G.: Influence of Splanchnic Nerves on Gastric Secretion, *Proc. Soc. Exper. Biol. & Med.* 29:511 (Jan.) 1932.

Histologic observations on the dog's stomach have been made by several investigators. Lim<sup>3</sup> recently found that the fundus comprises most of the stomach and that the cardiac and pyloric regions, with their mucous-secreting glands, are relatively small. In distinction to the structure of the mucosa of the stomach of man, oxyntic cells were found in both the cardiac and the pyloric region, although in the latter they were small and primitive.

These observations have been verified physiologically by the use of pouches made in various portions of the stomach. Pavlov<sup>4</sup> and other investigators repeatedly have demonstrated that the fundic portion secretes acid, while Ivy and Oyama<sup>4</sup> have shown by a similar technic that the secretion of the pyloric region is mucoid and slightly alkaline.

Resection of the acid-secreting mucous membrane in an attempt to reduce gastric acidity was tried by Mann.<sup>5</sup> He reported that in dogs, by diversion of the secretion poured into the duodenum, he could produce peptic ulcers which developed much more slowly and which became indurated more than usual if he removed most of the fundic portion of the stomach, leaving a narrow gastric tube with an intact lesser curvature connecting the esophagus and duodenum.

Deloyers and Johnson<sup>6</sup> investigated the secretory changes following the removal of a large amount of the fundic mucosa of dogs. They resected the greater curvature of the stomach, leaving only the cardiac region, the "air pocket," a narrow gastric tube consisting chiefly of lesser curvature and the antrum. Observations with test meals, made from the tenth to the twentieth day after operation, disclosed a definite reduction in concentration of both free and total hydrochloric acid.

Connell,<sup>7</sup> also working with dogs, performed a similar operation which he termed fundusectomy. Observations were made on the concentration of free acid, on the total acidity and on the emptying time of the stomach. Following the operation there was a primary delay in the emptying time, with a return to normal in about six weeks. There was also a reduction in both the concentration of free acid and the

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3. Lim, R. K. S.: The Gastric Mucosa, *Quart. J. Micr. Sc.* **66**:187 (June) 1922.

4. Ivy, A. C., and Oyama, Y.: Secretion of the Pars Pylorica Gastri, *Am. J. Physiol.* **57**:51 (Aug.) 1921.

5. Mann, F. C.: Chemical and Mechanical Factors in the Experimentally Produced Peptic Ulcer, *Tr. A. Am. Physicians* **42**:224, 1927.

6. Deloyers, Lucien, and Johnson, J. W. S. A.: Recherches sur la topographie des régions élaboratrices de l'acide chlorhydrique dans l'estomac, *Presse méd.* **37**: 879 (July 6) 1929.

7. Connell, F. G.: (a) Fundusectomy: A New Principle in the Treatment of Gastric or Duodenal Ulcer, *Surg., Gynec. & Obst.* **49**:696 (Nov.) 1929; (b) Fundusectomy: Experimental, *ibid.* **53**:750 (Dec.) 1931; (c) Resection of the Fundus of the Stomach for Peptic Ulcer, *Ann. Surg.* **92**:200 (Aug.) 1932.

total acidity, with a gradual return of the latter to the normal pre-operative level in about three months. The value for free acid remained low. On the basis of these results he concluded that partial fundusectomy might be of therapeutic value in the treatment of certain types of peptic ulcer.

#### PROCEDURE

Five dogs were used in this series of experiments. In each of the five dogs gastric and duodenal fistulas were made after the method of Mann and Bollman,<sup>8</sup> in order that specimens of the gastric and duodenal content could be easily and rapidly secured as frequently as desired. In each instance the duodenal fistula



Fig. 1.—Gastric and duodenal fistulas made after the method of Mann and Bollman.

was placed on the anterior surface of the second portion of the duodenum at the level of the head of the pancreas, while the gastric fistula was placed on the anterior surface of the stomach, either in the region of the antrum or high on the cardia (fig. 1). In all surgical procedures general anesthesia and the usual surgical technic were used.

Two series of control experiments were done. The dogs were made to fast eighteen hours. Then the maximal response in gastric acidity as well as changes in the hydrogen ion concentration of the duodenal content were noted in all five animals (1) after the feeding of 100 Gm. of raw meat and (2) after subcutaneous injection

8. Mann, F. C., and Bollman, J. L.: A Method for Making a Satisfactory Fistula at Any Level of the Gastro-Intestinal Tract, *Ann. Surg.* 93:794 (March) 1931.



of 1 mg. of histamine. To this end, aspirations of the gastric and duodenal content were made at fixed intervals—every hour in the experiments in which a meat meal was used and every fifteen minutes in the experiments in which histamine was used—and aspirations at these intervals were continued until the readings had returned to approximately the value during fasting. The hydrogen ion concentration of the gastric and of the duodenal content was determined by means of the quinhydrone gold electrode with a Leeds and Northrup potentiometer.<sup>9</sup> A sufficient amount of gastric content was aspirated each time to permit the determination of values for free acid and for total acidity; titrations were run against tenth-normal sodium hydroxide with Töpfer's reagent and phenolphthalein as indicators. Each experiment was repeated a sufficient number of times to determine the normal range of reaction and to suggest accuracy of the results.



Fig. 2.—Fundus resected after gastric and duodenal fistulas had been made.

The emptying time of the stomach of each animal also was determined with 250 cc. of a 20 per cent mixture of barium sulphate in water and observations under the fluoroscope at intervals until the stomach was empty.

After a reliable set of results had been obtained in the control experiments a second operation was performed in which most of the greater curvature of the stomach and varying amounts of the fundus, ranging from one half to four fifths of the total fundus, were resected (fig. 2). The cardia, antrum and lesser curvature were left intact. The experiments with the meat meal and with histamine were repeated from two to seven weeks and from fifteen to eighteen weeks after the operation, and the results were compared with those obtained in the control experiments. Observations on emptying time also were repeated.

9. Clark, W. M.: *The Determination of Hydrogen Ions*, Baltimore, Williams & Wilkins Company, 1920.

## RESULTS

In analyzing the results only the maximal acid response of the stomach and the maximal effect of this response on the reaction of the duodenal content were used in each experiment. A comparison of the results obtained before removal of part of the fundus with those obtained after removal of part of the fundus should thus indicate any alteration in the ability of the stomach to respond maximally to the stimuli employed.

*Gastric Hydrogen Ion Concentration.*—Changes in the gastric hydrogen ion concentration following fundusectomy were at best only

TABLE 1.—*Changes in Hydrogen Ion Concentration of Gastric and Duodenal Content After Removal of Varying Amounts of Fundic Mucosa*

Stimulus	Dog	Approximate Amount of Fundus Removed	<i>p</i> <sub>H</sub>		
			Control	2 to 7 Weeks After Operation	15 to 18 Weeks After Operation
Gastric Content					
100 Gm. meat by mouth	1	1/2	1.29-1.69	1.65-1.34-1.17	1.41-1.37
	2	1/2	1.31-1.34	1.51-1.34-1.37	1.68-1.41
	3	2/3	1.24-2.54	1.63-1.46	
	4	4/5	1.32-1.33	1.32-1.49-1.51	1.32-1.46
	5	4/5	1.23-1.23	2.20-1.49	1.37-1.73
1 mg. histamine subcutaneously	1	1/2	1.07-1.33	1.22-1.17	1.40-1.40
	2	1/2	1.07-1.12	1.29-1.17	1.09-1.16
	3	2/3	1.23-1.28	1.12-1.17	
	4	4/5	1.10-1.12	1.32-1.26	1.26-1.33
	5	4/5	1.02-1.05	1.12-1.37-1.20	1.17
Duodenal Content					
100 Gm. meat by mouth	1	1/2	4.10-4.49	4.34-4.59-3.11	4.73-4.71
	2	1/2	4.04-4.92	4.81-5.18-4.44	5.06-3.78
	3	2/3	4.04-5.24	6.00-5.18	
	4	4/5	3.62-3.39	4.15-3.15-4.12	3.69-3.78
	5	4/5	4.23-4.42	3.10-5.67	
1 mg. histamine subcutaneously	1	1/2	2.90-5.98	5.98-5.41	6.57-4.66
	2	1/2	5.47-6.49	5.93-5.41	1.80-6.12
	3	2/3	6.07-7.38	7.12-7.27	
	4	4/5	1.39-5.24	5.17-5.29	2.10-2.26
	5	4/5	4.50-6.39	5.46-6.48-6.63	

slight in most of the experiments and were consistently seen in only two dogs, from which approximately four fifths of the fundus had been removed (table 1).

*Duodenal Hydrogen Ion Concentration.*—The duodenal hydrogen ion concentration was only slightly affected by fundusectomy, and the changes that did occur were inconstant. Alterations occurred more frequently after the meat meal and were rarely seen after the administration of histamine (table 1).

*Free Acid.*—The concentration of free acid in the gastric content of one animal (dog 3) was not changed following fundusectomy when either meat or histamine was given. Two animals (dogs 1 and 2) sometimes gave evidence of a reduction of free acidity of the gastric content after histamine had been given and sometimes after meat had

been given; reduction was not an invariable occurrence nor was it consistent. Free acidity of the gastric content of the two remaining of the five animals (dogs 4 and 5) was reduced in almost all instances after the administration of either meat or histamine. From both of these two animals approximately four fifths of the fundus had been removed. Late observations on these last animals in most instances disclosed less marked reduction in the value for free acid than had been obtained from two to seven weeks after fundusectomy (table 2).

*Total Acidity.*—Total acidity of the gastric content of one dog (dog 3) was not changed after fundusectomy following the meat meal

TABLE 2.—*Maximal Response in Concentration of Free Acid and in Total Acidity of the Gastric Content \**

Stimulus	Dog	Approximate Amount of Fundus Removed	Control	2 to 7 Weeks After Operation	15 to 18 Weeks After Operation
Free Acid					
100 Gm. meat	1	1/2	40.0-75.0	35.0-60.0-90.0	70.0-70.0
	2	1/2	65.0-85.0	50.0-60.0-60.0	42.5-65.0
	3	2/3	45.0-60.0	45.0-45.0	
	4	4/5	75.0-77.5	72.5-50.0-52.5	70.0-92.5
	5	4/5	90.0-90.0	10.0-55.0	70.0-37.5
1 mg. histamine	1	1/2	125.0-140.0	85.0-90.0	70.0-92.5
	2	1/2	121.0-123.0	70.0-96.0	124.0-108.0
	3	2/3	87.0-111.0	110.0-88.0	
	4	4/5	108.0-115.0	68.0-71.0	80.0-72.0
	5	4/5	116.0-129.0	100.0-65.0-92.0	90.0
Total Acidity					
100 Gm. meat	1	1/2	120.0-140.0	100.0-130.0-137.5	142.5-160.0
	2	1/2	125.0-140.0	110.0-120.0-120.0	132.5-195.0
	3	2/3	155.0-170.0	170.0-185.0	
	4	4/5	145.0-155.0	95.0-115.0-127.0	125.0-162.5
	5	4/5	160.0-165.0	80.0-120.0	135.0-140.0
1 mg. histamine	1	1/2	138.0-150.0	102.5-104.0	105.0-122.5
	2	1/2	131.0-133.0	85.0-108.0	166.0-142.0
	3	2/3	100.0-125.0	124.0-106.0	
	4	4/5	120.0-125.0	56.0- 93.0	103.0-102.0
	5	4/5	128.0-141.0	114.0- 75.0-108.0	110.0

\* Estimated by Töpfer's method.

or after the administration of histamine; another (dog 1) gave no evidence of change after the injection of meat but showed a definite reduction after the administration of histamine, while a third (dog 2) gave evidence of definite reduction in the early observations after the ingestion of meat and after the administration of histamine, but later normal values returned irrespective of whether meat or histamine had been given. The two dogs from which approximately four fifths of the fundus had been removed continued to give evidence of some reduction in total acidity throughout the whole series of observations, although the reduction in the value for total acid in most instances was not so marked in the late observations (table 2).

*Relation Between the Amount of Fundus Removed and the Effect on Gastric Acidity.*—It is evident that there is some correlation between the

amount of fundus removed and the subsequent effect on gastric acidity, for only in the two dogs from which approximately four fifths of the fundus had been removed were alterations consistently found in the gastric hydrogen ion concentration, concentration of free acid and total acidity, while in the three dogs from which smaller amounts had been removed there were slight or only occasional changes. No such correlation could be detected, however, in the group in which smaller amounts of fundic mucosa were removed. Thus, one dog, from which approximately two thirds of the fundus had been removed, gave no evidence of changes in the gastric hydrogen ion concentration, free acid or total acidity, while the other two, from which tissue estimated to represent approximately one half of the fundus had been removed, gave evidence of occasional changes. Failure to find any correlation here possibly results from the difficulty of accurately estimating the amount of tissue removed. That there was a difference between the amount of fundus removed from the dogs which consistently gave evidence of change and the amount removed from those which gave no evidence of change or of only occasional change is certain, for from the former as much of the fundus was removed as was possible, while in the latter fundic tissue that could have been removed was allowed to remain.

*Emptying Time.*—Fluoroscopic examination of the stomach of the dogs in the control observations disclosed that the emptying time varied between one hour and twenty minutes and two hours. Following fundusectomy there was acceleration of the emptying time of the stomach in most of the dogs, with a gradual return to normal in from fifteen to eighteen weeks. In two of the dogs there was a slight delay in emptying of the stomach.

#### COMMENT

Although the results of any study of gastric acidity are likely to be open to question because of the wide variations that can occur, the usual objections seem scarcely valid if only the maximal response to a definite stimulus is used. The use of two different types of stimuli was resorted to, more with the idea of having two different sets of results to check against each other than because of any special merits of the one over the other.

The results obtained in these experiments appear to confirm most of the work of other investigators. The experimental ulcers obtained by Mann and Bollman<sup>8</sup> when fundusectomy was performed at the same time as, or preceding, surgical duodenal drainage indicate that the increased degree of chronicity which these authors noted was the result of reduction in the amount of acid produced in the stomach, even though this was not sufficient entirely to prevent the formation or

development of the ulcers. The results of Deloyers and Johnson<sup>6</sup> and those of Connell<sup>7b</sup> as well as mine clearly show that there is a reduction in both the concentration of free acid and in total acidity immediately following operation, when most of the fundic mucosa has been removed.

Connell,<sup>7b</sup> in his observations which extended over a period of three months, found that the concentration of free acid remained reduced but that total acidity returned to normal. I found this phenomenon in only one dog from which approximately one half of the fundus had been removed, and even with this animal the result was obtained only in experiments with the meat meal; following the administration of histamine values for both free acid and total acidity were normal in the later observations. In the gastric content of dogs from which approximately four fifths of the fundic mucosa was removed there was persistent reduction of both the concentration of free acid and the total acidity throughout the whole course of the experiment, although reduction of either total or free acidity was usually not as marked in the late as in the early observations. In most instances the differences between early and late results were roughly the same both for the concentration of free acid and for the total acidity, and any alteration in the one was reflected in the other.

This reduction in the acidity of the gastric content undoubtedly results from the quantitative diminution in the secretion of acid brought about by the removal of a large portion of the acid-secreting fundus. Attempts to prove such quantitative changes were made in the histamine tests, and at each aspiration an effort was made to withdraw and measure all the secretion present in the stomach. Although I could never be certain that I had aspirated all the secretion present, the amount obtained at the height of the reaction after fundusectomy was definitely less than the amount secured before fundusectomy. As a rule the reduction in concentration of free acid was more marked than the reduction in total acidity. This would indicate that after fundusectomy the gastric content has relatively an increased amount of acid existing in the combined form and that this may result from alteration in the ratio of the amount of mucus and acid secreted, for the antrum and cardia remain untouched by the operation, and thus the amount of mucus secreted should remain unchanged.

Failure of gastric acidity to change at all or more than occasionally after resection of approximately one half to two thirds of the fundic mucosa and its failure to change more than moderately after the removal of a still greater amount attest to the fact that the stomach possesses that same wide factor of safety that is possessed by so many other organs of the body, permitting it to act almost normally even after extensive resection of its acid-secreting tissue. The value of such a procedure in

surgical treatment of those conditions of man which demand reduction in gastric acidity can be properly determined only by its direct application.

#### SUMMARY

The changes in gastric acidity were studied before and after resection of varying amounts of fundic mucosa. Alterations in gastric acidity as determined by changes in the hydrogen ion concentration were very slight, while alterations in the hydrogen ion concentration of duodenal content were rarely seen. Definite reductions in both concentration of free acid and total acidity were noted immediately after operation in those dogs in which extensive resection was performed, but in subsequent observations at the end of four months the changes were less marked.

# WOUND HEALING AFTER ANTERIOR GASTRO-ENTEROSTOMY

## II. FATE OF MUCOSAL INCLUSIONS AND THEIR PREVENTION; DESCRIPTION OF A NEW SUTURE TECHNIC. AN EXPERIMENTAL STUDY IN DOGS

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In a previous experimental study<sup>1</sup> we attempted to reproduce serosal inclusions such as are found at times on the female parietal and visceral peritoneum and showed that when two serosal surfaces are brought together as in a gastro-enterostomy no recognizable serosal inclusions (celomic epithelium) are formed. This result was not unexpected in view of the studies of Ranvier and Marchand,<sup>2</sup> Cunningham,<sup>3</sup> Foot<sup>4</sup> and others. However, we believed it possible that such inclusions might have been overlooked when an investigator was engrossed in some other phase of the problem of the behavior of celomic epithelium. As noted, our search in this respect was fruitless.

On the other hand, we did find that when we employed suture methods on the anterior aspect of gastro-intestinal anastomoses that everted mucosa into the line of apposition between stomach and intestine, then mucosal inclusions (appositional rests or inclusions) similar to

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Our experiments and observations were completed in January 1931, and the substance of this paper was reported at a meeting of the North Pacific Surgical Society, Dec. 3, 1931. Illness has prevented prior publication.

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2. Ranvier and Marchand, quoted by Cunningham.<sup>3</sup>

3. Cunningham, R. S.: The Changes in the Omentum of the Rabbit During Mild Irritations, with Special Reference to the Specificity of the Mesothelium, *Bull. Johns Hop'ins Hosp.* **33**:257, 1922.

4. Foot, N. C.: Studies on Endothelial Reactions: V. The Endothelium in the Healing of Aptic Wounds in the Omentum of Rabbits, *J. Exper. Med.* **34**:625, 1921.

those shown in figures 2, 3 and 4 occurred between their walls and were observable for as long as twenty days after operation. This was particularly noticeable when the innermost suture on the anterior aspect of the anastomosis was a continuous, through-and-through circular stitch (technic 5) which is commonly recommended in surgical textbooks<sup>1</sup> (fig. 1).

Another type of mucosal inclusion was observed to occur about silk serosubmucosal sutures when they pierced the intestinal mucosa. These we termed "suture inclusions" in contradistinction to the aforementioned appositional inclusions.

We also observed that most rapid and uncomplicated healing from mucosa to serosa on the anterior aspect of a gastro-intestinal anastomosis

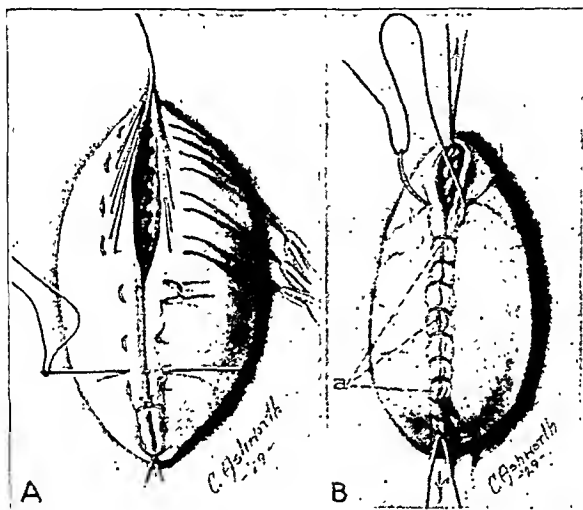


Fig. 1.—*A* is a demonstration of suture method 4, the Halsted presection suture technic, used only on the anterior aspect of the ostium. *B* is a demonstration of suture method 5, the ordinary continuous circular through-and-through suture which when used anteriorly inevitably causes macroscopic mucosal eversion as shown at *a* (Martzloff and Suckow<sup>1</sup>).

occurred with the Halsted presection suture method, which for the sake of brevity we have referred to as technic 4. With this method the sutures are in the serosubmucosa (fig. 1), and the mucosa therefore is neither sewed nor everted. All these observations were made and confirmed on two separate series of dogs.

In this study which was begun after our first two series had been completed we have had as our purpose three principal objects: (1) to repeat, on a third and separate series of animals, the finding of mucosal inclusions in the anterior line of apposition of gastro-intestinal anastomoses after the use of the ordinary through-and-through circular con-



tinuous suture (technic 5); (2) to study the fate of these appositional inclusions after a longer period of healing (ninety days), and (3) to develop a practical two layer suture method that would permit approximately the rapid healing obtained by the one layer Halsted presection suture method and at the same time eliminate some of the objectionable features of the other multilayer suture methods that are generally used on the anterior aspects of gastro-enterostomy ostia.

The present study was carried out on twenty-two dogs. Two of these died of bronchopneumonia (autopsy) on the third postoperative day during an epidemic of "snuffles," leaving twenty animals available for the observations reported here.

#### TECHNIC AND OBSERVATIONS ON RESULTS

In five dogs (nos. 54, 59, 60, 63 and 72) suture technic 5 was used, and healing was studied nine, fourteen, twenty, thirty-one and thirty-four days after operation. In view of the protocols given in our previous study we omit them here, because this series substantiates our earlier observations on the effect of this suture method on the anterior aspect of gastro-intestinal anastomoses. Briefly, appositional mucosal inclusions were well developed in one animal (no. 60) twenty days after operation, and some small deeply placed glands were found in the line of apposition nine days after operation in dog 72. In the latter animal there was also a well defined defect with a pyogenic membrane on the mucosal aspect of the apposed stomach and intestine where mucosal regeneration had not occurred. In dog 59, after fourteen days we could not be certain whether a well developed mucosal inclusion was appositional or a suture inclusion.

In three animals (nos. 54, 60 and 63) well marked silk suture defects lined by intestinal mucosa (suture inclusions) were encountered in the wall of the intestine. In a fourth animal (no. 59), previously noted, the origin of a mucosal inclusion was debatable.

In other words, the observations in our first report have been confirmed: Suture technics, particularly the continuous through-and-through circular suture (method 5), by which gastro-intestinal mucosa is everted, cause mucosal inclusions in the line of apposition in an appreciable proportion of experimental animals. The question of mucosal inclusions caused by silk suture is another matter and, as we have pointed out, depends on the nicety and precision with which silk sutures are placed. This in turn is in part dependent on the degree of distortion the preceding suture has given to the line of anastomosis. In the entire present series of twenty animals, when silk suture inclusions occurred they were on the intestinal side of the anastomosis.

*Fate of Mucosal Inclusions.*—In order to see whether the mucosal inclusions we had observed in the anterior aspect of gastro-intestinal anastomoses actually persist, eight dogs (nos. 53, 55, 56, 57, 58, 66, 69 and 73) were operated on and killed after a period of from ninety to ninety-seven days. In each instance an innermost continuous circular through-and-through suture of plain 00 catgut (technic 5) was used on the anterior aspect of the gastro-intestinal anastomosis, followed by a second row of interrupted mattress sutures (Halsted's) of 0 black silk. This was identical with technic 5 used in each of our previous experimental series.

Large mucosal inclusions in the line of apposition (appositional inclusions) were observed in four animals (nos. 53, 56, 57 and 73). Serial sections were made and studied in three of the animals killed after ninety days (nos. 53, 56 and 57) and in three other animals (nos. 45, 49 and 54) belonging to an earlier series. Observations made on the latter after healing periods of fourteen, twenty and thirty-four days, respectively, following the same suture technic (method 5) were included in our first report. However, serial sections were not available at that time. Our protocols covering observations on the animals killed after ninety days are given here in briefest outline.

Dog 53 (ninety-day healing period).—Mucosal healing was complete with the formation of glands up to the point where the two layers of mucosae (gastric and intestinal) unite. The point of transition was abrupt, and gastric parietal cells extended up to and stopped abruptly where the mucus-secreting cells of the intestinal mucosa began. The muscularis of the stomach and that of the intestine were united by, and frayed out into, a broad zone of connective tissue. There was a well defined mucosal inclusion in the line of apposition. This had a glandular structure and membrana propria characteristic of intestinal mucosa. There was no definite cellular infiltration about this inclusion. Farther out toward the serosa was a definite though moderate infiltration of round and polymorphonuclear cells. The mucosal inclusion in serial section finally effected a free communication with the gastro-intestinal lumen. In its deepest ramification (slide 5) the mucosa of the inclusion minus the muscularis mucosae penetrated almost the entire thickness of the circular muscularis and lay within 1 mm. of the serosa as an excessively deep gastro-intestinal crypt, in the depths of which gastric and intestinal mucosa meet.

Dog 55 (ninety-day healing period).—Mucosal healing was complete, as in dog 53. Mucosal marginal cysts were seen on the intestinal side of the line of mucosal apposition. The muscular layers of the stomach and intestine were united by a narrow zone of connective tissue. A silk suture in the intestinal wall was immediately surrounded by monocytes and recognizable fibroblasts. In one place a multinuclear giant cell occurred, while only an occasional lymphocyte or polymorphonuclear leukocyte was seen. A dense fibrous stroma in turn surrounded all this. No mucosal inclusions were seen. We would consider this a good end-result.

Dog 56 (ninety-day healing period).—Sections showed excellent restitution at the point of gastro-intestinal mucosal apposition. However, farther out in the line of apposition was a large bilocular mucosal inclusion lined by a flattened layer of epithelium (fig. 2). External (toward the serosa) to this was another mucosal inclusion lined by intestinal epithelium containing a silk thread and some exudate and communicating with the intestinal lumen at a point about 1 cm. distant from the point of gastro-intestinal mucosal apposition. There was a moderate infiltration of round and polymorphonuclear cells about this suture inclusion which had the appearance of an interstitial diverticulum. Where this inclusion communicated with the intestine there were a marked loss of intestinal mucosa and a marked eosinophilic infiltration into the remains of the basement membrane. There was not, however, sufficient histologic evidence to warrant the conclusion that this mucosal loss was entirely due to ulceration. More likely it represented, in part at least, a technical artefact due to sectioning. In serial sections this inclusion showed considerable change in form, but no distention. The appositional inclusion first mentioned in serial section showed other septums crossing its lumen so that it was multilocular. At no time did it communicate with the gastro-intestinal lumen.

Dog 57 (ninety-day healing period).—Mucosal healing was excellent. A glandular mucosal inclusion surrounded by compact fibrous stroma was seen right in the line of apposition within 1 mm. of the serosa. The adjacent subserosa showed moderate infiltration by round and polymorphonuclear cells. On the gastric side of the line of apposition was a mucosal inclusion with a surrounding leukocytic infiltration which resembled a suture inclusion, but no silk was seen. However, the presence of large monocytic cells and large spindle-shaped cells (fibroblasts)



Fig. 2 (dog 56, method 5, ninety day healing period).—This shows two types of mucosal inclusions. At *b* is an appositional mucosal inclusion which is bilocular, distended and lined by a smooth layer of flattened epithelium. In serial sections this inclusion shows other septumis, remains distended and does not communicate with the gastro-intestinal lumen. At *c* is a mucosal inclusion lined by a single layer of mucosa and associated with a silk suture (suture inclusion). It contains exudate, is surrounded by inflammatory reaction and communicates with the intestinal lumen (*I*) where there is a large mucosal defect that is explained in the text. *S* indicates the wall of the stomach. Gastric and intestinal mucosa meet at *a*.

was typical of the reaction ordinarily seen about silk. This inclusion appeared to come from the gastric mucosa since the muscularis mucosae at this point showed an interruption with a few typical gastric glands lying in the submucosa but not in communication with the inclusion. This inclusion represented the only probable

suture inclusion we had seen involving the stomach, and we were unable to find it in our serial sections.

Serial sections, however, did show the aforementioned appositional inclusion in brief communication with the gastro-intestinal lumen. The inclusion (fig. 3) possessed a complex glandular structure resembling intestinal mucosa, and the gastro-intestinal mucosa overlying it showed marked loss of substance and a well defined inflammatory reaction. In serial sections from another block another set of appositional inclusions were seen (fig. 4). These contained exudate and had an obliquely burrowing, tortuous communication, 0.5 cm. long, with the gastro-intestinal lumen at the point of union with the gastro-intestinal mucosa. This communication was again lost, so that the ultimate result was a mucosal sinus

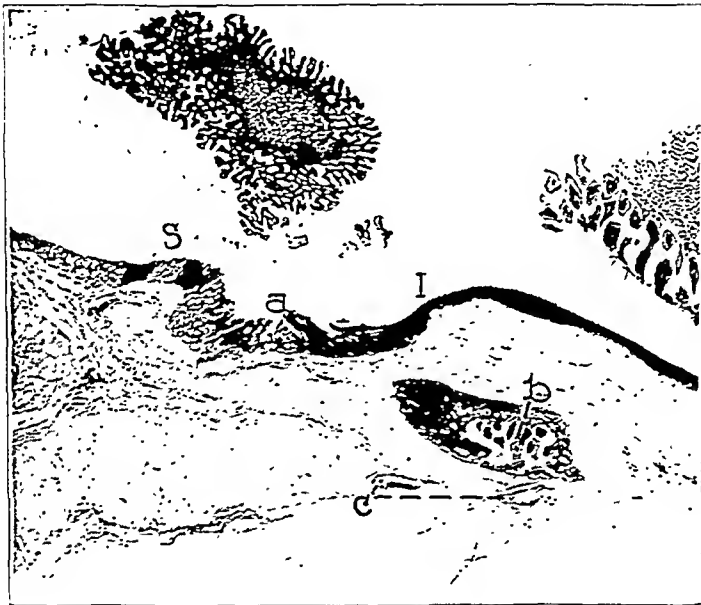


Fig. 3 (dog 57, method 5, ninety day healing period).—*a* is the point where the gastric and intestinal mucosa meet; *b* is a glandular appositional mucosal inclusion between the wall of the stomach (*S*) and that of the intestine (*I*) with a surrounding inflammatory reaction. The mucosa of the stomach and of the intestine show loss of substance and inflammatory reaction (other sections show this inclusion communicating with the gastro-intestinal lumen). Silk sutures in the wall escaping into the peritoneal cavity are indicated by *c*.

which extended in two directions from a central communication with the gastro-intestinal lumen. No recognizable gastric mucosa was seen in the inclusion. The deeper portion of the inclusion maintained a position close to the serosa. A large marginal cyst on the gastric side of the line of apposition remained intact and did not communicate with the gastro-intestinal lumen.

Dog 58 (ninety-day healing period).—Healing at the point of gastro-intestinal mucosal apposition was abnormal as compared with the other animals examined after ninety days. The mucosa was shallow and devoid of glands; some exudate was seen in the lumen, and there was an infiltration of the neighboring papillae

by polymorphonuclear cells. There was also an infiltration by round and polymorphonuclear cells extending from the mucosa into the connective tissue that united the walls of the stomach and the intestine. All this was due to a silk suture in the muscularis of the intestine which had worked its way into the gastro-intestinal lumen at the line of apposition. No mucosal inclusions were seen.

Dog 66 (ninety-four day healing period).—Observations on the sections were irrelevant except for some marginal cysts in the gastric mucosa and a long, narrow mucosal inclusion in the muscularis of the intestine well to one side of the line of apposition. Because of its position we recognized this as a suture inclusion, although no silk was seen associated with it. The line of gastro-intestinal apposition showed a moderate amount of scar tissue. Two silk sutures in this area showed a moderate infiltration by round and polymorphonuclear cells in addition

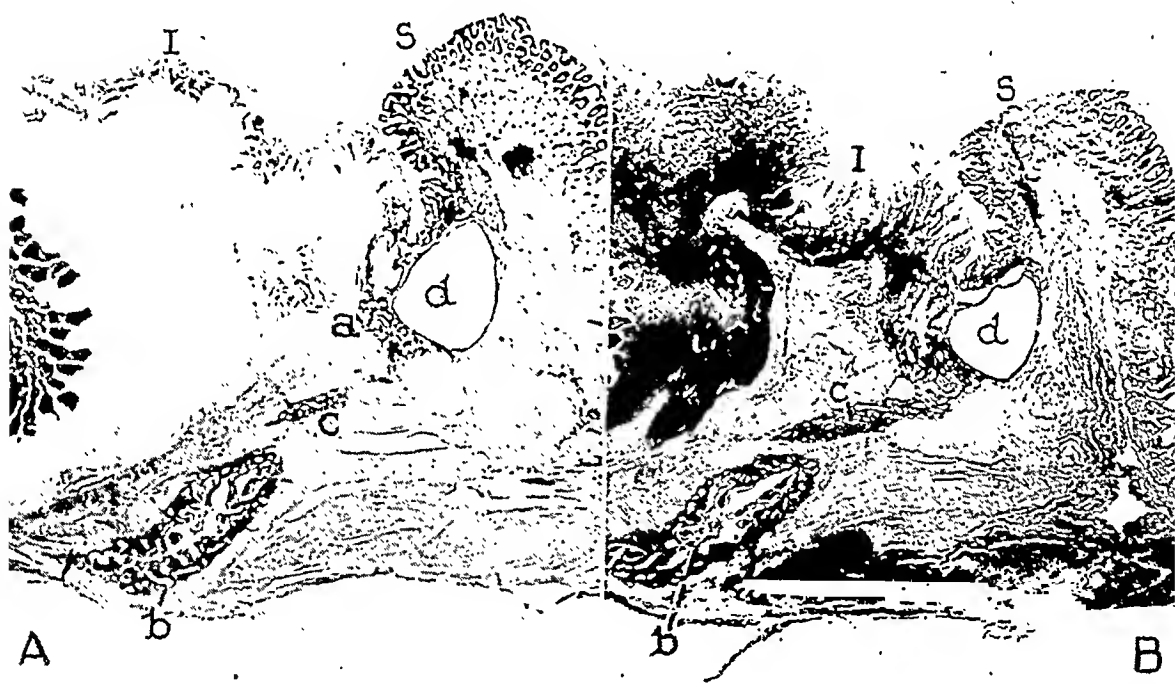


Fig. 4 (dog 57).—In *A* the glandular appositional inclusion at *b* is not a continuation of the one shown in figure 3. At *c* another glandular inclusion is seen. A large marginal cyst is seen at *d* which does not communicate with the gastro-intestinal lumen. In *B* the appositional inclusion (*c*) communicates with the gastro-intestinal lumen. Sections farther along in the block showed inclusion *b* joining with *c* and so communicating with the gastro-intestinal lumen. *I* and *S* indicate intestine and stomach, respectively.

to the customary large monocytic cells that immediately surrounded the fragmented silk. There was also moderate infiltration of the subserosa by round and polymorphonuclear cells.

Dog 69 (ninety-day healing period).—Observations on the sections were essentially irrelevant except for some silk suture defects near the line of apposition which contained exudate and an infiltration by surrounding round and polymorphonuclear cells. On the basis of previous experience it is a fair assumption that this suture communicated with the gastro-intestinal lumen at some point, although the

sections did not show it and serial sections were not made. There was a moderate infiltration into the subserosa by round cells.

Dog 73 (ninety-seven day healing period).—Observations on the sections were irrelevant except for a mucosal inclusion in the line of apposition. This measured 0.5 cm. in diameter and had a basement membrane and intestinal villi in places, some of the villi showing aggregations of polymorphonuclear leukocytes. The inclusion extended to within 1.5 mm. of the serosa, and there was a definite though moderate cellular infiltration containing some plasma cells in the subserosa. A marginal cyst was seen right in the line of gastric and intestinal mucosal apposition.

Dogs 45, 49 and 54 (fourteen, twenty and thirty-four day healing periods).—Observations on serial sections merely confirmed our previous observations. In dog 45 a glandular inclusion in the line of anastomosis (appositional inclusion)

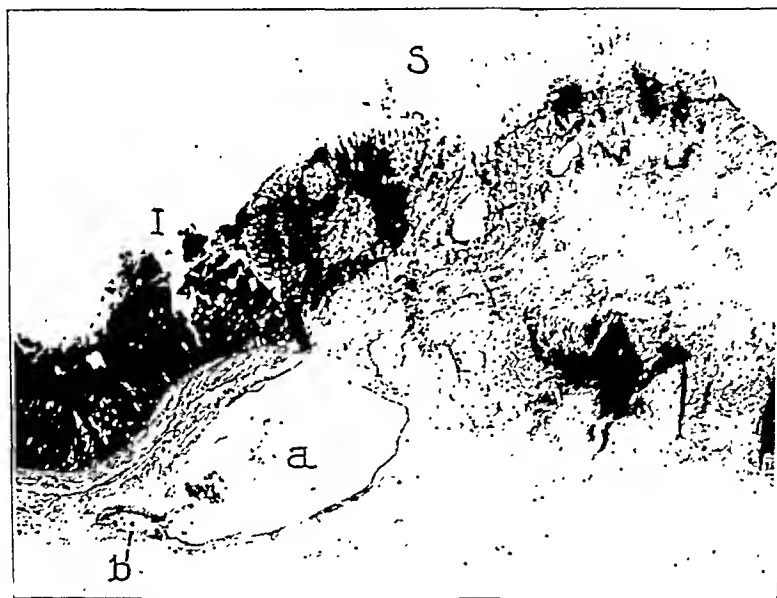


Fig. 5 (dog 54, method 5, thirty-four day healing period).—This section shows a cystic suture (?) inclusion (*a*) which is distended and in serial section shows no communication with the gastro-intestinal lumen. The inclusion contained silk, exudate and a low columnar epithelial lining membrane. There was an inflammatory reaction about the inclusion. A sinus (*b*) lined by granulation tissue and a pyogenic membrane communicated with the cystic structure (*a*). *S* indicates necrotic gastric mucosa and *I*, intestinal mucosa.

did not develop a communication with the gastro-intestinal lumen. This inclusion was not seen in the sections studied for our first report but came to light after the block was cut into for the purpose of tracing a suture inclusion. In dog 49 the appositional inclusion reported in our first paper was found to have developed a communication with the gastro-intestinal lumen and to disappear, being replaced by an area of marked inflammatory reaction. A suture inclusion in the wall of the intestine showed no opening into the intestine although it was involved in a pronounced inflammatory process, and the suture, judging from the course of the

inflammatory reaction, was discharging into the peritoneal cavity. However, we did not actually demonstrate this. In dog 54 the large mucosal inclusion about a silk suture in the intestinal wall, reported in our first paper, remained distended and contained exudate and in serial section was not found to communicate with the intestinal lumen (fig. 5). In fact, this inclusion apparently occurred right in the line of apposition. Whether it was primarily an appositional inclusion or a suture inclusion one cannot say, for it is possible that the silk suture was incorporated in an appositional inclusion.

#### COMMENT

The results obtained on this series of animals confirm our previous observation that suture methods which tend to evert the mucosa into the line of apposition in gastro-intestinal anastomoses cause mucosal inclusions in an appreciable number of animals (50 per cent in this series). These inclusions persist, for they were found ninety days after operation, and when they do not establish a communication with the gastro-intestinal lumen they may form cysts of appreciable size. When, however, an inclusion does open into the gastro-intestinal lumen the communication in our specimens has been narrow in comparison with the size of the inclusion, and dilatation of the inclusion did not occur. In some specimens these inclusions were accompanied by inflammatory phenomena after a ninety day period of healing. This we judge to be definitely pathologic when we consider that anastomoses performed by suture methods which are not complicated by mucosal eversion show an almost complete absence of inflammatory phenomena after a healing period of twenty days or less. Appositional mucosal inclusions, therefore, are undesirable complications even though our observations did not indicate any more untoward effects than those we have described.

#### SUTURE METHODS

*Connell's and Halsted's Method.*—The suture methods with which we obtained no appositional mucosal inclusions in our previous study were the Connell suture and the Halsted presection suture method. The former is a two layer suture method in which the first suture layer along the anterior aspect of the gastro-intestinal ostium is a through-and-through continuous right-angled catgut stitch that does not cross the free mucosal margins. As far as our experimental observations are concerned the suture is practical and satisfactory, although it is associated with considerable inflammation and delayed mucosal healing as compared with the Halsted method. However, with the exception of the latter we consider it superior to any of the multilayer suture methods from the standpoint of its practical application and ultimate healing. The Halsted presection method is a one layer suture method used on the anterior aspect of the gastro-intestinal anastomosis which avoids suture eversion or purposeful penetration of the mucosa.

In this method a number of Halsted's serosubmucosal mattress sutures of 0 black silk are loosely placed before the stomach and intestine are opened. These presection sutures are retracted, the stomach and intestine are incised and a suture of catgut (second posterior layer) is placed through all thicknesses of the stomach and intestine for hemostasis on the posterior aspect of the ostium. Bleeding points on the anterior aspect of the ostium are ligated individually. The presection sutures are now drawn up and tied and any additional sutures are placed where needed. This, as we previously reported, results in perfect infolding of the gastro-intestinal mucosa and serosa, absence of mucosal inclusions in the line of apposition, and a rapidity of healing that surpasses that of any of the other methods used. A practical disadvantage which this method has is that it may become very bunglesome if the operating team is not familiar with its technic, while a two layer suture technic avoids this fault. For this reason and because many surgeons depend on at least one suture-line for hemostasis along the anterior aspect of the ostium methods calling for two and sometimes three layers of sutures are commonly employed.

*Three Layer Suture Method.*—On the basis of our reported experimental observations<sup>1</sup> we can see no advantage to a three layer suture technic which has the disadvantage of an additional technical step and the excessive use of suture material. The separate suturing of the mucosa (mucosa and submucosa) which a three layer technic ordinarily employs does not in our experience hasten mucosal union but is rather a retarding factor when compared with methods which do not require suturing of the mucosa.

*Anterior Method 7 (Two Layer Serosubmucosal Suture).*—In order to have a simple and practical two layer suture method for the anterior aspect of a gastro-intestinal anastomosis which would avoid eversion of the mucosa with consequent formation of appositional mucosal inclusions and suture trauma to the mucosal margins and at the same time provide hemostasis to control capillary oozing (not important bleeding points, which should be ligated) and would permit rapid and uncomplicated healing comparable to that obtained with the Halsted presection method, we employed a suture method we have not heretofore seen described. This method we believe fulfils the requirements we have mentioned, and we have referred to it in our protocols as anterior method 7. It is actually a two layer serosubmucosal suture.

The catgut suture (00 plain) which has been used posteriorly as the innermost layer is continued anteriorly as the innermost anterior layer to unite the stomach and the intestine. The suture is carried on a fine, curved or straight intestinal needle which is always directed obliquely toward the cut edge of the stomach or intestine and in the



direction of the unsutured defect, as shown in figure 6. The needle is inserted about 0.5 cm. from the cut edge of the viscus. It should penetrate only as deeply as the outermost layers of the submucosa and should come out at the cut edge of the viscus so as to pierce the muscularis and avoid the cut edge of the mucosa. The latter point may sound like a highly theoretical and unpractical refinement. As a matter of fact, it is a relatively simple and practical procedure, as we have found experimentally and on patients.

However, the first proposition, i. e., placing this suture only as deep as the outermost layers of the submucosa, is open to technical criticism. Obviously insertion of intestinal sutures with a curved needle on a needle holder makes accurate placement in the outer layers of the sub-

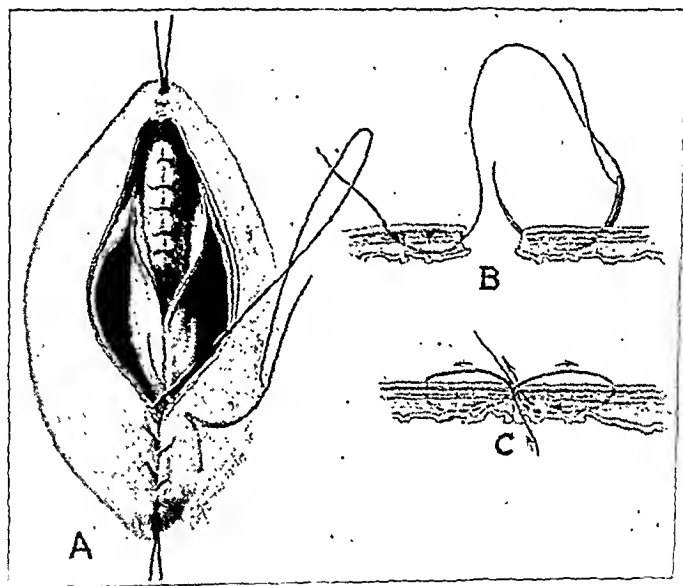


Fig. 6.—A demonstration of our two layer serosubmucosal suture (anterior method 7) with an ordinary serosubmucosal suture (*A*) used posteriorly while the mucosa is not sutured. Normally the mucosal edges fall together. This procedure we consider relatively impracticable, as described in the text. Anteriorly the suture we have described is shown. *B* and *C* are self explanatory and illustrate in cross-section the suture which permits healing that is almost as uncomplicated and rapid as that which follows the single layer Halsted presection technic (method 4). The anterior suture layer in *A* is drawn up more closely than is illustrated in *A* and *C* so as to cause serosal inversion. This is then reinforced by a layer of Halsted's mattress sutures which are not illustrated.

mucosa impossible. Therefore, penetration of the mucosa, particularly on the thin-walled intestinal side, is a relatively common though not serious fault when catgut is used. When the suture is tensed it brings the cut edges of the stomach and intestine together as shown in figure 6 *c*. Further tension inverts the serosa, and further inversion is effected by a second row of Halsted's silk mattress sutures which

complete the anastomosis. Care is taken during this procedure to avoid instrumental trauma to the mucosa. The edges of the cut viscera are therefore manipulated by 'grasping the seromuscular layer with fine mouse-tooth forceps. Everting mucosa is readily inverted by an assistant with any suitable instrument with a smooth surface.

We cannot understand the rationale of resecting the so-called redundant mucosa, for it apparently plays a rôle in covering the surgical defect, and its resection would apparently create defects greater than those we have demonstrated in our previous report. However, we have produced no direct evidence to support this assumption. Five animals (nos. 70, 71, 74, 75 and 76) were employed for gastro-intestinal anastomosis in which our two layer serosubmucosal inverting suture (anterior method 7) was used on the anterior aspect of the ostium. One animal died of pneumonia on the second postoperative day (day after operation) and this specimen was not studied.

After six days, counting the day of operation as the first postoperative day, specimens (dog 74) showed that the line of mucosal apposition was nowhere actually devoid of mucosa. However, the gastric mucosa, while present at and near the line of apposition, was low and definitely damaged, showing a moderate infiltration by polymorphonuclear cells and some overlying exudate. Except at the point of apposition the mucosa lay on a recognizable muscularis mucosae. Right at the point of gastro-intestinal mucosal apposition new gastric mucosal cells joined the relatively undisturbed intestinal epithelium. Farther away (from 1 to 2 mm.) from the point of apposition on the gastric side was a small defect about 2 mm. long which was devoid of a covering epithelium, but scattered through this small zone which contained granulation tissue were viable mucosal cells. The intestinal mucosa near the line of apposition also showed some loss of substance which was limited to the superficial layers. Proceeding out toward the serosa along the line of apposition rather compact young fibrous stroma was seen. This was almost devoid of cellular infiltration except where the remains of a catgut suture was associated with a dense polymorphonuclear exudate. Farther out near the serosa the intestinal wall contained a silk suture defect with a glandular mucosal suture inclusion and an associated intense inflammatory reaction.

Specimens from dog 76 showed better mucosal healing than those from dog 74. Gastric and intestinal mucosa showed a glandular structure and only a superficial disturbance (figs. 7 and 8). At the point of mucosal apposition was an area, a fraction of a millimeter in length, devoid of epithelium. The muscularis mucosae on both sides extended up to the point of apposition. On the intestinal side about 2 mm. from the point of mucosal apposition the muscularis mucosae and mucosa showed an abrupt interruption for about 1 mm. Here the overlying

mucosa was lost, and the remaining portion showed distortion and cellular infiltration which extended into the superficial portion of the submucosa. We believe that this indicates an area where the catgut suture was passed too deeply. Farther out in the line of apposition



Fig. 7 (dog 76, anterior method 7, six day healing period).—The point of gastric (*s*) and intestinal (*I*) mucosal apposition is shown at *a* where there is a small area devoid of epithelium and a small long plug of exudate at *b*. *X* indicates a small area devoid of intestinal mucosa composed of a hyaline-appearing zone with some cellular infiltration lying on the muscularis mucosae. Silk threads are indicated at *c* near the serosa. The photomicrograph has been retouched to bring out the boundaries between the gastric and intestinal mucosa and their underlying submucosa.

between the stomach and the intestine excellent healing had occurred, with less cellular infiltration than in dog 74. The silk sutures in these sections showed almost total absence of surrounding inflammatory phenomena.

A nine day specimen (dog 70) showed remarkable mucosal union. The mucosa was of about normal thickness and had a glandular structure which, however, showed distinct alteration (figs. 10 and 11). The muscularis mucosae of the stomach and intestine was intact up to the point of mucosal apposition. Farther out in the line of apposition between the stomach and intestine was compact fibrous union with little



Fig. 8.—A higher magnification of the area of mucosal apposition shown in figure 7. At *a* is the small area devoid of epithelium at a point of gastric and intestinal mucosal apposition. *I* indicates intestine, *s*, stomach, and *b* a plug of exudate.

cellular infiltration except around some silk sutures which were associated with an intense cellular infiltration and a mucosal inclusion on the intestinal side.

Results after a healing period of fourteen days (dog 71) were merely an improvement on those in dog 70. Union along the line of apposition was compact and without cellular infiltration except around the broken up, hyaline-appearing remains of a catgut suture which was associated with a moderate infiltration by round cells. No silk was seen.

The healing, both mucosal and interstitial, following the use of our serosubmucosal two layer inverting suture (method 7) on the anterior aspect of the gastro-intestinal anastomosis surpasses that obtained by any other method we have used except the one layer Halsted presection method (method 4). In addition, the method eliminates the undesirable appositional mucosal inclusions and lends additional support to our observation that suture of the mucosa is not only superfluous but undoubtedly complicates and retards rapid healing.



Fig. 9 (dog 21, method 4 [Halsted's presection method] six day healing period).—This section is shown to compare with figure 7. At *a* is a point of gastric (*S*) and intestinal (*I*) mucosal union completely covered by epithelium. *X* indicates two lymph follicle-like aggregations of round cells. Healing in the line of apposition from the mucosa to the serosa was excellent.

*Posterior Suture Methods.*—These were discussed in our previous paper and observations on this series add no further information. We should state that an adaptation of anterior method 7 to the innermost posterior aspect of the anastomosis, while it results in rapid and surpassingly excellent healing, is essentially impracticable because it does

not produce hemostasis and is difficult to place accurately, while practically equally good healing is obtained by the use of the ordinary continuous through-and-through circular suture (posterior method 5). The latter does not cause the undesirable complications here that occur when it is used on the anterior aspect of the anastomosis.

As far as remote results are concerned, in our specimens after ninety days of healing, we could see no distinctive difference in the healing



Fig. 10 (dog 70, anterior method 7, nine day healing period).—A section showing remarkable mucosal restitution at *a*. The small cystic areas opposite *S* indicate an area of gastric mucosa damaged probably from our catgut suture. This appearance is characteristic of trauma by suture (probably also of any other type of light mechanical trauma) to either gastric or intestinal mucosa. At *c* is a silk suture defect with a surrounding inflammatory reaction. This also involves *b* where the silk lies in a space lined by intestinal mucosa (suture inclusion) (fig. 11). *I* indicates intestine.

which followed the use of the lock-stitch suture and that which followed posterior methods 5 and 7 as the innermost posterior layers. It will be remembered that healing after the lock-stitch suture, as reported in

our previous study, was complicated by an appreciable loss of mucosa and considerable inflammatory reaction at and about the point of gastro-intestinal apposition during the early stages of healing. In all our specimens after ninety days of healing the muscularis mucosae remained separated by a definite zone of fibrous stroma. However, the other muscular layers in some specimens, particularly after posterior method 7, showed such little intervening fibrous stroma that it was difficult to see. In other specimens gastric and intestinal muscularis were separated by an easily distinguishable zone of connective tissue.

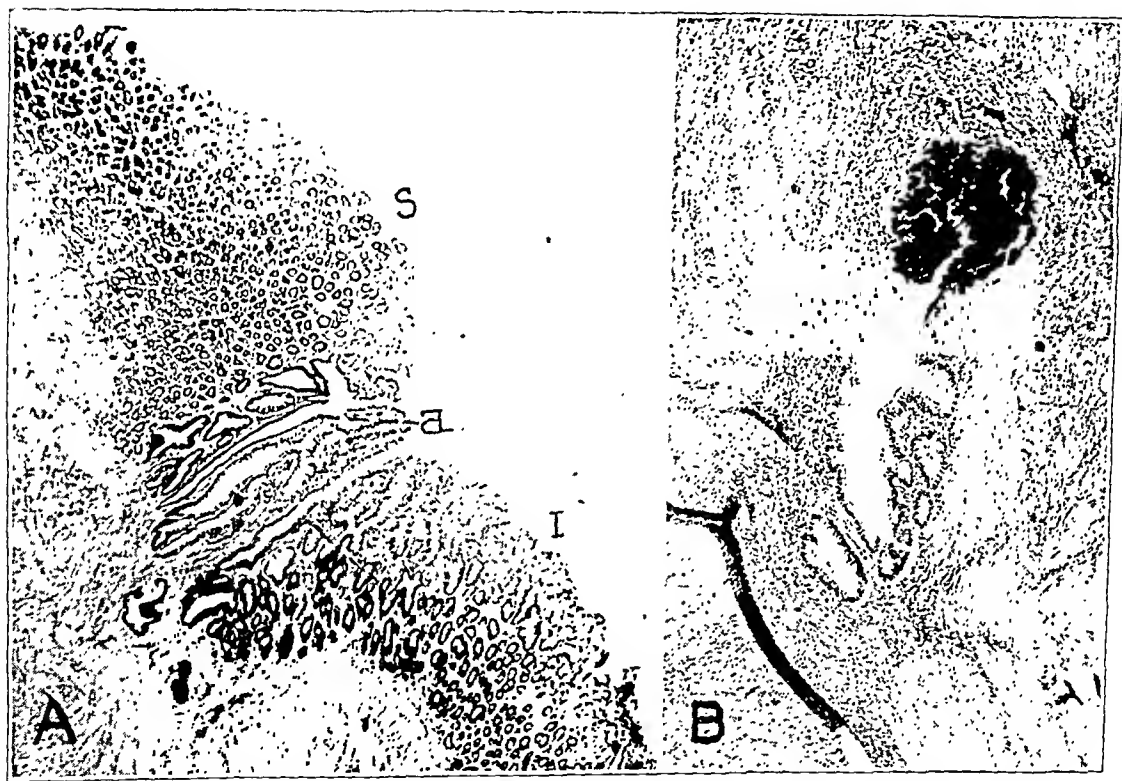


Fig. 11.—*A* is a higher magnification of the corresponding area in figure 10. The exact point where the gastric (*S*) and intestinal (*I*) mucosa meet is shown at *a*. *B* is higher magnification of the area *b* in figure 10.

#### THE FATE OF SILK SUTURES

This was considered in our former study and we shall consider here only the fate of silk sutures in the eight animals in which there was a healing period of ninety days. Histologic study of the material from the anterior aspect of the gastro-intestinal ostium showed silk suture material in six of the eight specimens. In one a mucosal inclusion was seen about the silk and in two others this was questionable. In five of the six specimens in which silk was observed there was a well defined active inflammatory reaction about the silk, and in three (nos. 57, 66

and 69) this was associated with chronic peritonitis. It could be definitely observed that silk was escaping into the gastro-intestinal lumen in two animals. In the others it was debatable in which direction the silk was moving; however, in view of the associated inflammation we suspected that the intestinal mucosa had been damaged and that the silk would ultimately find its way into the gastro-intestinal lumen.

A study of the posterior aspect of the gastro-intestinal ostium in seven specimens offered an interesting contrast. It will be remembered that posterior suturing was done by placing first a continuous circular serosubmucosal suture of 0 black silk with a curved intestinal needle on a needle holder. In other words, this silk suture was not placed by the most desirable technic. The second posterior suture was placed after the stomach and intestine were opened and in five animals consisted of a continuous lock-stitch suture of 00 plain catgut that traversed the entire thickness of the wall of the stomach and intestine, while in two animals this second row of catgut suture was merely a continuous circular suture that passed through the serosa and muscularis, possibly some submucosa, but avoided the mucosa.

Remains of silk sutures were seen in all seven specimens after posterior suture, and in none was an associated mucosal inclusion observed. In two specimens there was evidence of an active inflammatory process about the silk, in each of which it was suspected that the silk was migrating toward the intestinal lumen, and in one there was associated questionable chronic peritonitis. In the five remaining specimens the silk was obviously migrating toward the serosa, frequently being seen in the subserosa and unassociated with any evidence of active inflammatory reaction such as lymphocytes and polymorphonuclear leukocytes.

It therefore appears that 0 silk suture material may persist in a gastro-intestinal anastomosis for ninety days or more after operation and that the question of its being associated with an active inflammatory process depends probably on a complicating mucosal injury. In the latter event the suture probably eventually escapes into the gastro-intestinal lumen.

It may seem strange that the posterior silk sutures which were placed with a curved needle on a needle holder were associated with fewer complications (inflammation, mucosal inclusions, discharge into the gastro-intestinal lumen) than the anterior silk sutures which were threaded on straight milliner's needles and placed directly by hand without a needle holder, which is the more ideal method. Here again our explanation is that it is difficult to place a serosubmucosal suture accurately when suturing has to be done at right angles to a ridge, as occurs particularly when suture method 5 is used anteriorly. It is then difficult to place a second row of mattress sutures close to such a distor-



tion without piercing the intestinal mucosa. Burget and one of us (K. H. M.)<sup>5</sup> had a corroborative experience in an earlier study. The wall of the stomach, because of its greater thickness, does not offer the same technical hazard.

#### SUMMARY AND CONCLUSIONS

This study is based on experimental observations on twenty dogs. Anterior gastroduodenostomies and jejunostomies were performed by two suture methods while the suture material was uniform throughout. We were unable in this study as in our previous one to demonstrate the occurrence of serosal cysts between the two apposed serosal surfaces of a gastro-enterostomy.

Mucosal inclusions in the anterior line of gastro-intestinal apposition were frequent occurrences in this, as in our previous, study when suture methods were employed that evert the mucosa between the walls of the stomach and intestine. The only method employed for this purpose was a through-and-through continuous circular suture (method 5) recommended in numerous textbooks of surgery.

Inclusions so produced may persist for ninety days or longer and may or may not communicate with the gastro-intestinal lumen as demonstrated by serial sections. When such communication fails the mucosal inclusion becomes distended to form a cyst of appreciable size. Inflammatory phenomena may also accompany such appositional inclusions.

Suture methods that produce such inclusions, therefore, are faulty in that they produce anomalies and complications that can only be regarded as undesirable. In view of this experience we reiterate the conclusions expressed in our previous study that the recommendation of some authors to use suture methods that evert gastro-intestinal mucosa for purposes of hemostasis is dubious advice.

The use of a two layer serosubmucosal suture technic (method 7) as proposed by us is practical and largely eliminates the faults of the other multilayered suture methods commonly used on the anterior aspects of gastro-enterostomies. It also permits exceptionally rapid healing and confirms our earlier observation that separate suture of the mucosa (mucosa and submucosa) is wholly unnecessary for rapid healing since it actually retards rather than hastens mucosal restitution.

This study confirmed our previous observations on the use of silk suture material in gastro-enterostomy. When so placed that they do not penetrate the mucosa silk sutures are ideal, for they produce a minimal inflammatory reaction. However, when they penetrate the

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5. Martzloff, K. H., and Burget, G. E.: The Closed Intestinal Loop: III. Aseptic End-to-End Intestinal Anastomosis and a Method for Making a Closed Intestinal Loop Suitable for Physiologic Studies, *Arch. Surg.* **23**:26 (July) 1931.

intestinal mucosa, as occasionally happens even in expert hands, they become complicated by infection and inflammation and often by mucosal inclusions (suture inclusions), all of which may persist for ninety days or longer. We therefore doubt the advisability of using silk suture material in gastro-intestinal anastomosis.

NOTE.—A recent experimental study by Nogara (Nogara, G.: *Sulle modalità di cicatrizzazione delle ferite chirurgiche dello stomaco in rapporto alla tecnica di sutura impiegata*, *Arch. ital. di chir.* **36**:111, 1934) reveals the use of a sero-submucosal suture (Donati) which, while slightly differently placed than our stitch, nevertheless, embodies the same principles. Nogara reported excellent healing of the wound with this extramucosal suture as compared with the results of other methods and confirmed our experience that separate suture of the mucosa is not a requisite for rapid uncomplicated healing.

# EVENTRATION OF THE DIAPHRAGM

WITH A REPORT OF TWO CASES

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Eventration of the diaphragm is rare, and because of this fact we feel that every case is worthy of detailed study. It also seems desirable to review the literature.

The purpose of this paper is (1) to summarize the available knowledge of the disease with a discussion of the literature and (2) to present reports of 2 cases.

## REVIEW OF THE LITERATURE

### THE NAME

Eventration of the diaphragm clinically has come to mean a congenital or, occasionally, an acquired high or elevated position of one leaf of the diaphragm muscle, characterized pathologically by aplasia or atrophy of the muscle fibers of the affected side but with no break in the continuity of the muscle, which in the vast majority of cases produces symptoms suggesting a gastric, cardiac, pulmonary or pleuropulmonary origin.

The term eventration has been objected to by many on the grounds that the derivation of the word, namely, "e," meaning out, and "venter," meaning belly, in no sense gives an impression of the true pathologic process. The term apparently inappropriately describes the condition which exists. Königer<sup>1</sup> suggested the term idiopathic high-lying diaphragm. Other names suggested have been high diaphragm, relaxed diaphragm and insufficiency of the diaphragm, as listed by Reifenstein;<sup>2</sup> Lerche<sup>3</sup> preferred insufficiency; Hillejan<sup>4</sup> called the condition relaxation of the diaphragm and Bierman<sup>5</sup> described his case as one of "idiopathic eventration," presumably by inference suggesting another

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From the Departments of Medicine and Surgery of the George Washington University School of Medicine.

1. Königer: München. med. Wchnschr. **56**:282, 1909.
2. Reifenstein, E. C.: Am. J. M. Sc. **169**:668, 1925.
3. Lerche, W.: Surg., Gynec. & Obst. **34**:224, 1922.
4. Hillejan, A.: Zentralbl. f. Gynäk. **47**:1383 (Aug.) 1923.
5. Bierman, M. I.: Radiology **4**:122 (Feb.) 1925.

type having a known origin. Goriainova <sup>6</sup> did not suggest the use of any particular name but discussed at some length the question of a name, calling attention to the work of Vieting, who suggested the term relaxation, of Leichtenstein, who called the condition "a high level of the diaphragm," and of Morrison,<sup>7</sup> who felt that "Petit's disease" would pay full tribute to that eminent eighteenth century surgeon who is given credit for first describing the condition. In Lord's <sup>8</sup> article it was suggested that the condition be called elevation of the diaphragm, the derivation of the word again being cited.

It is well known that the term is incorrectly used and is a misnomer. If the original *eventratio diaphragmatica* were translated to be diaphragmatic eventration and interpreted to mean the belly (abdominal organs) moving out of its usual position and in a diaphragmatic direction there might be some justification for the term. We believe with others that it is to be regretted that the term eventration of the diaphragm has crept into the literature, but as the intended meaning is usually well understood it might be confusing to change; so usage condemns the term to remain.

#### HISTORY

The first authentic case was described by Petit <sup>9</sup> after a postmortem examination. The report of this case appeared in a posthumous edition of the author's work published in 1774 and edited by his pupil Lesne. Korns <sup>10</sup> called attention to the fact that Bowditch in 1853 mentioned Senac's case (1729) as being in all probability a genuine instance of eventration, but after reference to the original article Korns stated that such a conclusion was not justifiable in his opinion. In connection with the report of Petit's case it is of considerable interest to note the inaccuracies that are found in the literature and that are repeated even after a correction is made. For instance, many writers have credited Petit with reporting a case in the literature as well as with naming the condition. Beck <sup>11</sup> and others have stated that Petit reported his case in 1790. Jean Louis Petit was born on March 13, 1674, and died on April 20, 1750, nearly twenty-five years prior to the appearance of the report of the case in the literature. There were apparently four editions

6. Goriainova, R. J.: *Vestnik roentgenol. i radiol.* **6**:257, 1928.

7. Morrison, J. M. W.: *Arch. Radiol. & Electroth.* **27**:353 (May) 1922.

8. Lord, F. T.: *Eventration of the Diaphragm*, *Arch. Surg.* **14**:316 (Jan.) 1927.

9. Petit: *Traité des maladies chirurgicales*, Paris, T. F. Didotjeune, 1774, vol. 2, p. 266.

10. Korns, H. M.: *Diagnosis of Eventration of the Diaphragm*, *Arch. Int. Med.* **28**:192 (Aug.) 1921.

11. Beck, H. G.: *Ann. Clin. Med.* **1**:262 (May) 1923.

of his work. The first three were edited by Lesne and appeared in 1774, 1780 and 1790, respectively, while the fourth edition, edited by Sanson, was published in 1837.

The name eventration was given to the disease by Beclard, mentioned in the writings of Cruveilhier.<sup>12</sup> Wood and Wood<sup>13</sup> mentioned that Petit gave the name eventration to the condition, but this is apparently erroneous, as Petit made no reference to the term in his published writings. Korns substantiated the latter view, and one is inclined to agree with him, as his critical review is a splendid piece of material.

Marsh<sup>14</sup> in 1867 reported the first instance of a clinical examination and a correlation of clinical signs and autopsy observations. Reports of roentgen studies in cases of eventration began to appear about 1901. Widenmann<sup>15</sup> has been credited by some<sup>13</sup> with being the first to use roentgen rays in diagnosing the disease, while others have mentioned Struppler<sup>16</sup> as the first to rely on roentgen study. This confusion is undoubtedly due to a difference in the date of their publications, as Widenmann reported his studies in March 1901 and Struppler published his report in May of the same year.

Historically, the celebrated case of Freidrich Schneider is of much interest. This case was first mentioned in 1890 by Stinzing, according to Neumann.<sup>17</sup> From this time until 1912 the patient Schneider presented his diagnostic problem at many clinics. Hirsch<sup>18</sup> in 1900 examined him and from roentgen studies made a diagnosis of hernia of the diaphragm. Volkmann and Becker saw the patient and made a diagnosis of dextrocardia, according to Glässner.<sup>19</sup> In 1905 Hildebrand and Hess<sup>20</sup> first established a diagnosis, depending on Schlippe's procedure of measuring respiratory variations with intragastric pressure. Lotze<sup>21</sup> in 1906 confirmed Hirsch's diagnosis of hernia. In 1912 von Eggeling<sup>22</sup> made a report of the necropsy observations which supported the diagnosis of Hildebrand and Hess of eventration.

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12. Cruveilhier: *Anatomie pathologique du corps humain*, Paris, J. B. Baillière, 1829, vol. 1, book 17; *Traité d'anatomie pathologique générale*, Paris, J. B. Baillière & fils, 1849, vol. 1, p. 614.

13. Wood, W. B., and Wood, F. G.: *Lancet* **2**:392, 1931.

14. Marsh: *Lancet* **1**:298, 1867.

15. Widenmann: *Berl. klin. Wchnschr.* **38**:279, 1901.

16. Struppler: *Deutsches Arch. f. klin. Med.* **70**:1, 1901.

17. Neumann: *Deutsche med. Wchnschr.* **45**:905 and 937, 1919; *München. med. Wchnschr.* **64**:719, 1917.

18. Hirsch: *München. med. Wchnschr.* **47**:996, 1900.

19. Glässner: *Fortschr. r. d. Geb. d. Röntgenstrahlen* **24**:208, 1916; *München. med. Wchnschr.* **63**:19, 1916.

20. Hildebrand and Hess: *München. med. Wchnschr.* **52**:745, 1905.

21. Lotze: *Deutsche med. Wchnschr.* **32**:1662, 1906.

22. von Eggeling: *München. med. Wchnschr.* **59**:2284, 1912.

A case of eventration on the right side was first reported by Wieting<sup>23</sup> in 1906, in which there was associated hernia of the left leaf of the diaphragm. This, to the best of our knowledge, is the only case of its kind reported. Eppinger<sup>24</sup> in 1911 described the second case of eventration on the right side; Glässer in 1916, the third, and Bayne-Jones<sup>25</sup> in 1916, the fourth. The last-mentioned was the first case of eventration on the right side to be reported in the American literature and the second on either side. Sailer and Rhein<sup>26</sup> reporting the first in 1935.

The searching critical review by Korns<sup>27</sup> contained several points of interest: First, it was a résumé of all the literature on the subject up to the time of writing, analytically studied and severely criticized for errors, with corrections of the same errors. Second, special attention was given to the diagnosis of the condition. Third, interest was aroused in the condition from a physiologic standpoint when the author described a diagnostic sign based on the function of respiration and the anatomic structures involved therein. Fourth, the first case of definite associated aplasia of the lung on the involved side was presented. Much credit is due Korns for this article.

#### ETIOLOGY

There is no specific cause demonstrable for eventration of the diaphragm. It is apparently congenital, although many instances have been cited of cases of an acquired condition and of a condition associated with other pathologic conditions if not actually produced by them. The early literature on the etiology pointed more to its congenital nature, while reports of the past ten years seem to substantiate the theory of the acquired nature of the disease. Reich, quoted by Gorainova,<sup>8</sup> stated that eventration must be definitely and clearly distinguished from the high diaphragm produced by paralysis of the phrenic nerve, that by the term eventration of the diaphragm should be understood a high level of the diaphragm resulting from atrophy and degeneration of the musculature and that all cases in which there is injury of the phrenic nerve, due to trauma, pathologic changes in the lung and infectious processes, must be excluded. Some confusion seems to exist relative to the etiology, but we are of the opinion after a critical search of reported cases that we must accept the etiologic grouping of both congenital and acquired types.

23. Wieting: *Deutsche Ztschr. f. Chir.* 82:315, 1906.

24. Eppinger: *Allgemeine und spezielle Pathologie des Zwerchfells*, in Nachtragel, C. W. H.: *Spezielle Pathologie und Therapie* (suppl., Vienna, A. Helden, 1911.

25. Bayne-Jones, S.: Eventration of the Diaphragm, *Arch. Int. Med.* 17:231 (Feb.) 1916.

26. Sailer, J., and Rhein, R. D.: *Ann. J. M. Sc.* 159:668, 1935.

*Theory of Congenital Origin.*—The supporters of the theory of the congenital origin of eventration advance the following to substantiate their belief: first, the relative frequency of occurrence on the left side; second, the frequency of occurrence in the fetus and in new-born and young children; third, associated congenital anomalies, and, fourth, the absence of symptoms for a long time.

Of a total of 183 cases reviewed (65 reported by Korns and 118 reviewed from original sources by us) the left leaf of the diaphragm was affected in 165 and the right leaf in 18. Reifenstein and others suggested the protection of the liver as a possible reason for the preponderance of the condition on the left side and further advanced the suggestion that the left leaf is the last to close. Embryologically one may look to the blood supply of the developing organs. Cutler and Cooper,<sup>27</sup> in discussing this aspect of such deficiencies, called attention to the fact that the rôle of the liver as a protecting organ to the right side is an inadequate reason as the liver is formed under the septum transversum and during a large part of embryonic life protects the left side as much as the right. Also, they expressed the belief that the explanation of the preponderance of diaphragmatic lesions on the left side lies in the distribution of the vascular elements which play such an important rôle in the early formation of the embryo. Supporting this contention they advanced the following embryologic facts: First, the position of the pulmonary ridge of Moll and the pleuroperitoneal membrane is determined by the common cardinal veins. In the human embryo measuring 20 mm., the common cardinal vein on the right grows and forms the superior vena cava, while that on the left atrophies and disappears. It seems that this would cause a tendency to weakness of the left pleuroperitoneal membrane. Second, in the embryo measuring 2.5 mm. the liver becomes adherent to the wall of the dorsal body on the right to allow for the formation of the vein of the placenta vena cava, which becomes the inferior vena cava. Third, in the embryo measuring 3.5 mm. the tubal heart loops over to the right preparatory to the formation of the atria and ventricles. Fourth, in the embryo measuring 4.5 mm. the right half of the sinus venosus is observed to be growing much faster than the left. It seems possible that the vascular concentration in the region of the right side of the diaphragm would contribute to the strengthening and blocking of the pleuroperitoneal canal, while the atrophy of the common cardinal vein on the left would contribute to the weakening of the left half of the diaphragm.

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27. Cutler, E. C., and Cooper, H. S. F.: Congenital Deficiency of the Diaphragm, Arch. Surg. 8:506 (March) 1924.

In one group of 83 cases reported since 1921 were 30 cases of patients under 25 years of age, distributed according to age groups as follows:

Age	No. of Cases	Age	No. of Cases
New-born .....	5	10 years.....	3
1 year.....	2	11 years.....	2
2 years.....	1	12 years.....	2
3 years.....	1	14 years.....	2
5 years.....	1	16 years.....	2
6 years.....	1	21 years.....	2
8 years.....	2	22 years.....	1
9 years.....	1	23 years.....	1

This frequency of occurrence in the new-born and in young children seems to support the theory of a congenital origin.

The association of other congenital conditions increases the value of this theory. The presence of such conditions has been reported by many authors. Transposition of one or more of intra-abdominal organs was reported by Morris,<sup>28</sup> Lord<sup>8</sup> and others. Megacolon was present in the cases of eventration reported by Aronson and Quénu and Fatou.<sup>29</sup> Other abnormalities reported were aplasia of the lung,<sup>30</sup> hypospadias, undescended testis,<sup>31</sup> abnormally lobulated lungs,<sup>25</sup> rotation of the esophagus,<sup>21</sup> aortic hypoplasia and pseudolobulation of the upper lobe of the lung,<sup>32</sup> reduction in the size of the phrenic nerve and esophageal diverticula<sup>33</sup> and nonrotation of the stomach.<sup>34</sup> Uniform absence of evidence of compression of the contiguous lung has been emphasized as one of the strongest arguments in favor of congenital etiology of eventration of the diaphragm. Byloff, cited by Bayne-Jones,<sup>25</sup> spoke of eventration as a stigma of degeneration.

The absence of symptoms for a long time with the finding of such a marked chronic pathologic process has been offered by some as evidence of a congenital lesion. It is inferred that if this were an acquired disease symptoms should begin at the time of onset in all cases. In Whittington's<sup>35</sup> patient, aged 64, the symptoms began rather suddenly and the previous history was irrelevant in every respect, while in Thomp-

28. Morris: *Brit. J. Radiol.* **2**:85, 1929.

29. Quénu, J., and Fatou, E.: *J. de chir.* **24**:1 (July) 1924.

30. Caussade and Fatou: *Bull. et mém. Soc. méd. d. hôp. de Paris* **52**:246, 1928. Korns.<sup>10</sup>

31. Hess, J. H.: *M. Clin. North America* **8**:567 (Sept.) 1924.

32. Vigetti: *Rev. méd. del Rosario* **18**:502 (Dec.) 1928.

33. Marchal, Fatou and Heim de Balzac: *Bull. et mém. Soc. méd. d. hôp. de Paris* **48**:795, 1932.

34. Harris, L. I., and Stivelman, B. P.: Nonrotation of Stomach Simulating Spontaneous Hydropneumothorax, *J. A. M. A.* **89**:1836 (Nov. 26) 1927.

35. Whittington: *Boston M. & S. J.* **190**:244, 1924.



son's<sup>36</sup> patient, aged 54, the sudden onset of symptoms suggested cardiac failure. In Madinaveitra's<sup>37</sup> case the patient, aged 63, complained of mild indigestion for twelve years with an acute increase in the gastric symptoms of only six months' duration. Fatou and Heim de Balzac<sup>38</sup> reported the case of a patient, aged 59, whose symptoms began with an acute pain which simulated that of angina. Such examples illustrate the delayed onset of symptoms in cases of eventration proved to be congenital by pathologic study.

*Theory of Acquired Origin.*—Trauma, toxic origin from acute infectious diseases, pulmonary tuberculosis, subphrenic abscess, tumor of the mediastinum, chronic gastric disturbance, lesions of the phrenic nerve other than traumatic, pregnancy, thoracic growth, aneurysm of the aorta and subdiaphragmatic hydatid cyst have been reported in the literature as being either causative or associated factors. Reported cases illustrate these contentions. Lerche, although not reporting specific cases, mentioned typhoid, diphtheria, septicemia, nephritic erysipelas, pericarditis, endocarditis, rheumatic fever, Huntington's chorea, alcoholic neuritis, fracture or luxation of the spinal column, spondylitis, pachymeningitis, spinal hemorrhage and tumor of the spinal canal as etiologic background for eventration.

Cruveilhier first mentioned trauma as the cause of eventration. Neumann in 1919 suggested injury of the phrenic nerve. Allan<sup>39</sup> in giving the history of his patient mentioned that pain came on suddenly after the cranking of an automobile and that the patient had "ruptured both sides." Wheatley's<sup>40</sup> patient was in an automobile accident which suggested traumatic origin, but the author did not conclude that it was the causative factor. Bamber,<sup>41</sup> Bulmer<sup>42</sup> and Vigetti mentioned lifting of heavy objects in the history of their patients. In the case reported by Bulmer there was an associated gastric ulcer, while in Vigetti's case there were pulmonary tuberculosis and hypoplasia of the aorta. Fatou and his associates<sup>43</sup> stated that the patient whose case they reported had a history of thoracic contusion on the right side with symptoms dating from the time of the accident, but the left leaf of the diaphragm was elevated. D'Pierron's<sup>44</sup> patient was a man, aged 34, who had been

36. Thompson, A. P.: Birmingham M. Rev. 5:44 (Feb.) 1930.

37. Madinaveitra: Progresos de la clín. 35:243 (April) 1927.

38. Fatou and Heim de Balzac: J. de radiol. et d'électrol. 16:491 (Oct.) 1932.

39. Allan, W.: Virginia M. Monthly 47:305 (Oct.) 1920.

40. Wheatley, F. E.: Boston M. & S. J. 197:87 (July 21) 1927.

41. Bamber, J. M.: M. Clin. North America 2:771 (Nov.) 1927.

42. Bulmer: Birmingham M. Rev. 5:48 (Feb.) 1930.

43. Fatou; Prévost, L., and Prévost, F.: Bull. et mém. Soc. méd. d. hôp. de Paris 52:259, 1928.

44. d'Pierron: Arch. d'électric. méd. 39:322 (Aug.) 1929.

well until a fall six months previously, after which there was extreme dyspnea with suffocation, which continued. During the fall there was severe compression of the stomach, and the author believed that this was the etiologic factor. Wood and Wood mentioned trauma and cited a case but said there was only a temporary elevation. Kromeke, cited by Goriainova, explained the more frequent involvement of the left cupola by the peculiarity of the course of the left phrenic nerve, which runs definitely more anterolaterally than the right one for one seventh of its course and unwinds not only on the superior surface of the left leaf but also on the under-surface and therefore is more prone to trauma than the nerve on the right side.

Toxic origin from acute infectious diseases is a relatively rare occurrence. Fischer <sup>45</sup> mentioned a case in which eventration developed during convalescence from double pneumonia and typhoid, but no other cases have been found on careful search of the literature with the exception of a case reported by Goriainova in which symptoms appeared after an attack of measles.

Pulmonary tuberculosis has been noted in a number of cases of eventration. The exact relationship has not been definitely established. Morrison <sup>46</sup> in reporting 9 cases of paralysis of the phrenic nerve stated that the elevation of the diaphragm was due to a pathologic lesion involving this nerve and producing roentgenographically a picture synonymous with that of Petit's eventration. The first case he mentioned was that of a man 58 years old who had bronchitis and pulmonary tuberculosis; on postmortem examination the phrenic nerve was found to be involved in a mass of fibrous tissue. In the ninth case there was extensive tuberculosis of the left lung and to a lesser extent of the right lung with the left side of the diaphragm elevated and partially fixed. Caussade and Fatou performed an autopsy in a case in which they had diagnosed the condition three months previously as eventration and bilateral tuberculosis and confirmed their clinical impressions; they likewise found a congenitally dwarfed left lung. They concluded that eventration is not infrequent in tuberculous persons. In a second case reported by the same authors <sup>47</sup> the condition was clinically diagnosed as eventration and tuberculosis, although the report was admittedly incomplete. Goriainova's patient, in whom symptoms appeared following an attack of measles, had tuberculous broncho-adenitis. De Lacerda's <sup>48</sup> first patient had been perfectly well up to five months prior to consultation and then began to have hemoptysis followed in a few days by cough, which caused acute sharp pains at the base of the left lung.

45. Fischer, H.: *M. Rec.* 86:653, 1914.

46. Morrison: *Arch. Radiol. & Electroth.* 28:72 (Aug.) 1923.

47. Caussade and Fatou: *Bull. et mém. Soc. méd. d. hôp. de Paris* 52:254, 1928.

48. de Lacerda: *Lisboa méd.* 5: 213 (April) 1928.

The sputum gave a positive reaction to Koch's organism, and the diaphragm was elevated on the left. The second case reported by the same author was that of an army officer, aged 36, who for ten months had a clinical history of tuberculosis and an intense pain in the epigastrium and at the base of the thorax on the left side which seemed to be related to the ingestion of food. There was a previous history of syphilis. A diagnosis was made of eventration and pulmonary tuberculosis with a positive reaction of the sputum. Labbé and his co-workers<sup>49</sup> reported a case of eventration, pulmonary tuberculosis and partial pneumothorax in the same patient. In an autopsy report<sup>50</sup> made about a year later they confirmed the clinical observations and concluded that the eventration was probably not congenital but secondary to the pulmonary infection. It is rather interesting that Labbé<sup>51</sup> reported the same case again, thereby giving rise to some confusion until careful investigation revealed it to be the same. Vigetti's case, which has been noted previously, was terminated by a "galloping type of consumption," but the author concluded because of the congenital abnormalities found at autopsy that the tuberculosis was secondary and terminal. Allan's patient, mentioned earlier, was found on roentgenologic study to have a tuberculous focus in the apex of the right lung, and he died one year later of pulmonary tuberculosis.

Chronic gastric disturbance was noted in a number of cases of eventration. The associated lesions mentioned most often were peptic ulcer and gastric carcinoma. Quénu and Fatou<sup>29</sup> were emphatic in their statement that gastric lesions do not cause eventration but that, on the contrary, eventration predisposes one to organic lesions of the stomach. Their contention was not substantiated further than by the citation of the occurrence of cancer or ulcer in 11 of 18 cases in which there was surgical intervention. Buono<sup>52</sup> felt, however, that ulcerative and neoplastic diseases of the stomach cause superelevation of the diaphragm. Golob's<sup>53</sup> patient, who was operated on by Lilienthal, had a carcinoma at the cardiac end of the stomach with eventration on the right side. The patient in the seventh case of Morrison's first series<sup>46</sup> had a cancer of the stomach, but the diaphragm was only slightly elevated, and one would doubt from the description that this was a true case of eventration. Verbrycke<sup>54</sup> reported the case of a patient with perforated ulcer high on the lesser curvature of the stomach and

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49. Labbé, M.; Boulin, R.; Azérad, E., and Soulié, P.: *Bull. et mém. Soc. méd. d. hôp. de Paris* **54**:830, 1930.

50. Labbé: *Bull. et mém. Soc. méd. d. hôp. de Paris* **47**:468, 1931.

51. Labbé: *Arch. de mal. de l'app. digestif* **23**:241 (March) 1933.

52. Buono: *Riv. di radiol. e fis. med.* **2**:118 (March) 1930.

53. Golob, M.: *M. J. & Rec.* **124**:473 (Oct. 20) 1926.

54. Verbrycke, J. R., Jr.: *Surg., Gynec. & Obst.* **40**:415 (March) 1925.

a high diaphragm or, more accurately from the description given, a localized eventration. However, the subsequent history and the roentgenograms submitted cast some doubt on the authenticity of the case as one of true eventration.

Causation by or association with other conditions is less rare. Goriainova mentioned injury to the sympathetic nerve endings as a possible cause. He cited Hoffman and several other authors as believing aerophagia to be an etiologic factor. Jawara and Dumitresco-Mante<sup>55</sup> noted a case of considerable interest in which a hydatid cyst was found under the diaphragm on the right side at operation and was drained and sutured. About two weeks later roentgen study demonstrated an elevation of the diaphragm on the right side with apparent fluid in a new cyst, which was aspirated. Two years later the authors reported the patient cured, but stated that the movement of the diaphragm was reduced; they concluded with a question as to whether this was a case of true eventration or only of distention.

After a study of cases reported in the literature we feel that the weight of evidence seems to be undoubtedly in favor of a theory of congenital origin, but some few cases presented in favor of an acquired nature bear evidence of careful consideration and cannot be overlooked.

Embryologic developmental defects are always rare, and eventration of the diaphragm is a relatively rare condition. The last critical review of the literature, made by Korns in 1921, included 65 cases. Since that time we have been able to find 118 cases reported in the literature, bringing the total to 183, including our own cases reported in this communication. Korns divided his cases into two groups: (1) those in which the diagnosis was regarded as proved, and (2) those in which the diagnosis was not proved but was regarded as reasonably certain. His standard of measurement was strict. The cases in the first group included those in which the diagnosis was substantiated by necropsy, operation or the physiologic study of the muscles of respiration, while those in the latter group were apparently all the others. Following Korns' plan we have tabulated the cases as follows:

	Incidence	
	Left Side	Right Side
Korns' collection		
Group 1.....	18	4
Group 2.....	41	2
Subsequent cases		
Group 1.....	23	2
Group 2.....	83	10
Total .....	165	18

55. Jawara and Dumitresco-Mante: *Rev. méd.-chir. d. mal. du foie* 7:105 (March-April) 1932.

In this grouping we have considered 3 of Lord's cases as belonging to group 1 and all of Uspensky's, as they demonstrated the presence of Hoover's or Korns' sign. One of our cases is in group 1, for the diagnosis was verified at operation, while our other case is in group 2. We have included in group 2, 22 of the 41 cases reported by Dillon and 8 of those in Morrison's series of cases associated with injury to the phrenic nerve, 1 falling into group 1 because the diagnosis was proved at autopsy. The condition in Dillon's cases and in some of Morrison's might be questioned as not being true eventration but rather rudimentary elevation. We have felt that with this explanation we could include them in this study as cases of eventration.

*Occurrence.*—Lord mentioned finding only 4 instances in the course of 16,504 roentgen examinations at the Massachusetts General Hospital. It is believed, however, that eventration is not as rare as this report would indicate for there are cases which have never been recorded in the literature.

Eventration seems to occur more frequently in males than in females. Walton<sup>56</sup> said that it occurs four times more frequently in the former than in the latter. It is not known on what basis these data were presented; we have not been able to confirm such a preponderance. In the group of cases we have reviewed the ratio was approximately 4:3 in the cases in which the sex was given. In a number of cases of eventration occurring in the new-born the various authors did not mention the sex. Whittington mentioned the fact that roentgenologists believe it to be more common than the literature suggests.

#### PATHOLOGY

The pathologic observations in this disease might be placed in two groups: the changes in the diaphragm and the associated or accompanying pathologic process.

The diaphragm has been variously described, but there is no adequate and detailed picture in any of the reports, and microscopic study of sections is totally lacking. In all cases the diaphragm was found definitely and markedly elevated. In a few reports a rudimentary eventration was mentioned, meaning apparently a moderate elevation, but these few cases are not considered by us as true examples of the condition and therefore have been dropped from the group. Bayne-Jones' discussion of the pathology is quite complete. His report was based on a study of 22 cases which came to autopsy or operation and therefore should be considered as fairly reliable examples. He stated that in all cases there was a thin translucent membranous diaphragm. It was usually a layer of fibrous tissue containing some muscle fibers,

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56. Walton, H. J.: *Am. J. Roentgenol.* **11**:420 (May) 1924.

but in a few there was only a thin aponeurotic sheet. The diaphragm was opaque and whitish as distinguished from the red of normal muscle tissue. Sailer and Rhein mentioned the microscopic observation of numerous muscle fibers, although on gross examination their absence was noted, while Wieting spoke of the diaphragm as a fascia-like structure without muscle fibers. Benda mentioned lipomatous pseudohypertrophy of the diaphragm. Motzfeldt<sup>57</sup> said that the diaphragm showed atrophy and fatty changes. Verbruycke in his cases found a bluish-gray, very thin diaphragm which apparently lacked tone, while in 1 of Morrison's cases that came to operation there was a thinned out diaphragm of dense fibrous tissue. In our own case, as will be seen in the surgical report, there was a much thinned out diaphragm which was tense at all times. Eggers<sup>58</sup> demonstrated in his case localized eventration at the central tendon without, of course, a rent in the diaphragm. This last case is the only one of its kind reported in the literature.

Pathologic change in the phrenic nerve on the side affected has been noted. Bayne-Jones stated that the phrenic nerve may be reduced in size, but that it contains normal fibers with no evidence of degeneration in the nerve trunk or its nuclei. Marchal and his associates mentioned the reduction in the size of the phrenic nerve, but this was a quotation and not an observation on any of his presented cases. Morrison reported 9 cases of paralysis of the phrenic nerve in which the nerve was involved in a mass of fibrous tissue, while in another case the nerve was involved in a nodule of carcinoma; full descriptive postmortem studies were conspicuously absent. Hess spoke of injured phrenic nerves and anomalies, but we are unable to find any such pathologic process described in reported cases aside from the aforementioned suggestion.

The lungs show no evidence of compression. Abnormally lobulated lungs have been reported. Korn reported that his case was "the first in which aplasia of the lung has been shown to accompany the condition of eventration of the diaphragm." Vigetti, in a splendid necropsy report, found the lung on the affected side "reduced in size with a pseudolobulation of the upper lobe." Pulmonary tuberculosis is frequently associated with the condition, and in a case of Labbé's pneumothorax was present.

The heart and mediastinum in eventration on the left side are displaced from the usual position to the right side; no mention has been made in the reported cases of the position of these structures in eventration on the right side. A number of writers have persisted in calling this dextrocardia, but most recent authors have confirmed the impression

57. Motzfeldt: *Deutsche med. Wchnschr.* **57**:1006, 1910.

58. Eggers, C.: *J. Thoracic Surg.* **1**:41 (Oct.) 1931.

that there is rotation of the heart rather than true transposition of that organ.

Other pathologic changes and associated diseases noted are: Hirschsprung's disease, dilatation and malformation of the mesentery, transposition of the stomach and colon, familial hernia, intestinal obstruction, emphysema, atelectasis, bronchitis, asthma, ascites, malnutrition, ectopic testis, gastric volvulus, esophagotracheal fistula, aneurysm of the aorta, hypoplasia of the aorta, carcinoma of the mediastinal glands, neoplasm of the lungs, ulcerative colitis, esophageal diverticulum, subdiaphragmatic hydropneumocyst, hypospadias, diphtheria, poliomyelitis, progressive spinal muscular atrophy, influenza, nephritis and other infectious diseases.

#### SYMPTOMATOLOGY

Usually the symptoms appear insidiously and are of varying duration, but occasionally the onset is sudden.<sup>54</sup> The duration of the symptoms according to a study of cases abstracted from the literature is from two weeks to twenty years from the time of onset.

Symptoms vary tremendously and are not characteristic, but they are suggestive of the location of the lesion. There may be no definite symptoms.<sup>58a</sup> Symptoms may be divided into four groups: (1) respiratory, (2) gastro-intestinal, (3) circulatory and (4) general. This grouping is submitted after a careful study of the records of 118 cases reported since 1921. The gastro-intestinal and respiratory symptoms seemed to dominate the picture in a majority of cases.

Gastro-intestinal symptoms in the order of frequency were: pain in the abdomen, vomiting, pressure or weight in the stomach, gas, constipation, nausea, belching, loss of appetite, diarrhea, pain on swallowing, cramps and heart burn.

Respiratory symptoms in the order of their frequency of occurrence were as follows: dyspnea, pain in the chest, cough and wheezing.

Cardiac symptoms were: palpitation, cyanosis and tachycardia.

General symptoms were: loss of weight, fatigue or weakness, dizziness, sinking or fainting spells, pain down the arm on the affected side, malnutrition, edema of the lower extremities, insomnia, exhaustion, restlessness and numbness of the extremities.

It is undoubtedly true that the thoracic and abdominal symptoms were predominant in the majority of cases, although occasionally one sees a bizarre presentation of symptoms definitely suggesting other

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58a. Owen, C. C.: *Radiology* 18:361 (Feb.) 1932. Uspensky: *Brit. J. Radiol.* 1:197 (June) 1928. Blackford, L. M., and Booth, W. T.: *Dextrocardia Secondary to Eventration of Diaphragm: Report of Asymptomatic Case*, *J. A. M. A.* 98: 883 (March 12) 1932. Foster, P. S.: *Australian & New Zealand J. Surg.* 2:200 (Oct.) 1932. Morris.<sup>28</sup> Lord.<sup>8</sup>

diseases. Sometimes when other diseases are present the symptomatology of the latter is the main picture. It has been noted that displacement of the diaphragm leads to a displacement, and at times to a deformity, of all the organs in contact with the diaphragm, and therefore the symptomatology varies and depends on the organs plus the rapidity and extent of displacement. One author<sup>59</sup> grouped symptoms into those of dislocation, that is, symptoms arising from the dislocated organs, and those of dysfunction due to the improper function or the failure to function of the organs involved. In the order of frequency of occurrence, by groups it was found in the cases reported and reviewed by one of us that the gastro-intestinal symptoms predominated, with the respiratory symptoms next and the cardiac symptoms last. A number of writers have placed various symptoms under different headings, which gives rise to some confusion in analyzing the cases for statistical comparison. For example, we placed dyspnea in the respiratory group as we felt that it is a pulmonary symptom due to pressure rather than one arising from cardiac pathologic change or dysfunction, although it is correctly pointed out by some authors that the heart is considerably more sensitive to any mechanical influence than are the lungs.

There are no unusual features of the gastro-intestinal symptom. They are the symptoms one would expect from displacement and dysfunction of the organs involved.

The symptom of pain in the chest, mentioned under the respiratory group, together with pain down the arm of the affected side, mentioned under the group of general symptoms, may lead one to suspect an anginal condition involving the coronary arteries. No such condition was reported in any of the autopsy observations in the literature.

#### PHYSICAL CHANGES

A summary of the typical but not pathognomonic observations elicited on physical examination may be given briefly: On general examination labored breathing, mild or severe, with some evidence of cyanosis suggests the possible thoracic location of the disease. The main physical signs are limited to the affected side of the thorax and the adjacent abdominal area. Inspection discloses diminished movement of the affected side, Litten's sign is absent, and Korns' or Hoover's sign is present. Palpation confirms the impression of diminished movement and the presence of Korns' or Hoover's sign and reveals diminished tactile fremitus at the base of the lung posteriorly on the involved side. The apex beat of the heart is difficult of palpation and when present is abnormally close to the left sternal border. The normal resonant percussion note over the lower third to the lower half of

59. Dillon: *Ergebn. d. med. Strahlenforsch.* 3:289, 1928.



the lung on the side affected is absent. It is replaced posteriorly by a dull note and anteriorly by either a dull note or a definite tympanic note, depending on the amount of fluid contained in the stomach at the time of the examination. A tympanic note elicited anteriorly as high as from the fourth to the second left rib is quite suggestive of eventration on the left side. The percussion of the cardiac area of dulness in eventration on the left side demonstrates clearly that the right border of the heart is well beyond the right margin of the sternum while the left border is within the midclavicular or nipple line and may even be lost under the sternum. On auscultation the breath sounds and vocal resonance are usually diminished or absent over an area approximately corresponding to the height of the affected lesion of the diaphragm. Auscultation of the heart usually gives negative results, although there are reports of distant heart sounds, tachycardia, extra-systole and even auricular fibrillation, as shown in 1 of our cases. A succussion splash is usually evident and likewise a metallic tinkle or peristaltic gurgle over the lower anterior portion of the thorax on the side involved.

Scattered throughout the literature are numerous records showing departures from the usual physical changes just noted. In Bayne-Jones' case there was no displacement or evidence of enlargement of the cardiac area of dulness with eventration on the right side. Clopton<sup>60</sup> recorded normal physical changes except that the cardiac area of dulness was more to the right than in his first case. No physical changes in a case of eventration on the left side were reported by Morrison and Fatou and Heim de Balzac. Greenwald and Kaufman<sup>61</sup> reported no physical changes in a case on the right side. Caussade and Fatou reported the physical signs of pulmonary tuberculosis overshadowing all others or replacing the usual signs. Eggers stated that on inspection of the chest there was complete absence of expiratory excursion on the left side in a case of eventration of the left side of the diaphragm. Vigetti reported tachycardia in a case of eventration associated with tuberculosis. In a case of eventration on the right side Levick<sup>62</sup> noted a uniform enlargement of the left side of the chest anteriorly. Blackford and Booth frankly reported finding tympany over the affected portion of the chest anteriorly only on reexamination following roentgenologic study. Jewett<sup>63</sup> mentioned finding congestion of the superficial veins over the upper anterior surface of the wall of the chest. Harris and Stivelmann noted a lagging of the thorax on the right side with the

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60. Clopton, M. B.: *Ann. Surg.* **78**:154 (Aug.) 1923.

61. Greenwald, H. M., and Kaufman, J.: Congenital Nonrotation of the Stomach with Eventration, *Am. J. Dis. Child.* **35**:641 (April) 1928.

62. Levick, G. M.: *Proc. Roy. Soc. Med.* **20**:1318 (July) 1923.

63. Jewett, C. H.: *Clifton M. Bull.* **8**:30 (Oct.) 1922.

lower interspaces on the same side, and the basal aspect of this side of the chest was more prominent in a case of eventration of the right side, while Allan reported that the left side seemed swollen and lagged on respiratory motion in a case of eventration on the left side. Prieto<sup>64</sup> noted the following changes in his case: The thorax in front showed marked deformity, the sternum deviating to the left; the thorax on the right appeared more ample, the intercostal spaces showed no modification and auscultation revealed distant heart sounds. The physical signs of pleurisy have been noted by many<sup>65</sup> and have been a source of error in diagnosis and medical management.

#### ROENTGENOLOGIC OBSERVATIONS

It is interesting to note that the roentgen ray has brought to light many cases of eventration but from the standpoint of diagnosis has added confusion and has given rise to numerous contradictory statements in the literature. After careful study we have reached the following conclusions regarding the roentgenologic observations: First, there are no pathognomonic roentgen signs, by which we mean there are no observations on which one can base a positive diagnosis; second, there are a number of signs which may make one strongly suspect eventration and on which one may even make a tentative diagnosis; third, many signs stated to be evidence of eventration undoubtedly occur both in eventration and in hernia, and fourth, there are a number of signs reported by various authors which apparently occur as coincidental findings.

Those signs which lend strong presumptive evidence to a diagnosis of eventration are: an unbroken curved convex line from the lateral wall of the chest to the mediastinum; the so-called "cup and spill," "cascade type" or bilocular stomach, with the level of fluid in the stomach after the ingestion of barium sulphate always coinciding with the esophageal opening when the patient is in the erect position; and the presence of a line above, the gastric bubble being to the medial side and the colonic bubble to the lateral side, which can be seen passing from one organ to the other forming a triangle below and between these two hollow organs.

The unbroken convex line so frequently mentioned is supposedly the intact smooth arch of the diaphragm. Dioclès and Orléan<sup>66</sup> in discussing this arched line stated that it may be the omentum or the walls

64. Prieto: *Progresos de la clín.* **41:95** (Feb.) 1933.

65. Levine, S.: *Ann. Int. Med.* **5:1000** (Feb.) 1932. Vigetti,<sup>32</sup> Thompson,<sup>36</sup> Allan,<sup>39</sup> Bamber,<sup>41</sup> Greenwald and Kaufman.<sup>61</sup>

66. Dioclès, L., and Orléan, E.: *Bull. et mém. Soc. de radiol. méd. de France* **19:278**, 1931.

of a hernial sac, as in Schoenfeld's case, or the wall of the stomach, and therefore is not to be relied on. Eggers, on the other hand, made a diagnosis by roentgenogram in his case of eventration based solely on this observation. Lord, in discussing this sign, cited the experience of Lotze, who made a diagnosis of eventration based on the unbroken line but at autopsy found diaphragmatic hernia. Reifenstein mentioned this sign as being fairly reliable, and Morrison rather emphatically called it one of the cardinal roentgenographic signs of eventration, yet one cannot well accept this as being authentic when he made a gross error in saying that until the time of writing eventration had occurred on the left side in all cases except that of Eppinger. Morrison must not have exhaustively reviewed the literature before publishing his résumé of the subject. Dillon mentioned the high unbroken arch as a characteristic sign and said that at times only a glance under the fluoroscope was sufficient to make the proper diagnosis; however, it is evident that in certain cases the diagnosis was associated with more difficulties. Lightwood<sup>67</sup> spoke of a "double convex parallel line" above the stomach as having considerable diagnostic value if present on repeated examination.

The so-called "cup and spill" type of stomach is caused by rotation on a fixed pivot which draws the greater curvature up under the diaphragm. The level of the fluid when barium is given always coincides with the esophageal aperture in eventration, whereas in hernia it is likely to be on a plane above this opening. Moore and Kirklin<sup>68</sup> corroborated this with the statement that it is a practical point in differentiation. Labbé mentioned this type of stomach as an inverted U stomach, while Jaubert de Beaujeu<sup>69</sup> spoke of it as a bilocular wallet stomach.

The convex line of the diaphragm stretching across from the air-filled colon to the stomach, forming a triangle below and between these organs, would, if constant, be a splendid presumptive finding in favor of a diagnosis of eventration.

There is much discussion in the literature regarding the movement of the diaphragm on the affected side. We feel that the movement may be normal, diminished, absent or reversed in either eventration or hernia. Reifenstein, Morrison and others have expressed the belief that paradoxical movement strongly suggests eventration, and Morrison went so far as to call it a cardinal sign of eventration. Reversed or paradoxical movement of the diaphragm is sometimes spoken of as Kienböck's phenomenon. Lord reported reversed movement on forced

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67. Lightwood, R.: *Proc. Roy. Soc. Med.* **26**:133 (Dec.) 1932.

68. Moore, A. B., and Kirklin, B. R.: *Progressive Roentgenologic Diagnosis of Diaphragmatic Hernia*, *J. A. M. A.* **95**:1966 (Dec. 27) 1930.

69. Jaubert de Beaujeu: *J. de radiol. et d'électrol.* **13**:508 (Sept.) 1929.

inspiration in his first case and limited but normal movement in his second and third cases, while Morrison found reversed movement in all of his cases. Bierman likewise reported limited but normal excursion and added that the leaf of the diaphragm on the unaffected side seemed to compensate for the affected leaf. Walton found normal diaphragmatic excursion in his case but stated that paradoxical movement was present in both hernia and eventration. Ottosen<sup>70</sup> examined his patient three years after his first observation and recorded accurate measurements of the movements of both leaflets of the diaphragm. He found that the affected side moved normally on respiration, but that movement on excursion was 1 cm. while that of the unaffected side was 4 cm. It is interesting to note that Greenwald and Kaufman, writing as late as 1928, stated that paradoxical movements occur in hernia and inferred this to be the differentiating point in diagnosis. Botteri<sup>71</sup> found the diaphragm in his case to be immobile. Goriainova spoke of paradoxical movement on deep inspiration as Wellman's sign and stated that a positive Wellman sign gave sufficient grounds in all 3 of his cases for ruling out a diagnosis of diaphragmatic hernia. Blackford and Booth found Wellman's sign present in their case but implied a different interpretation, stating that movement was paradoxical on deep thoracic inspiration but normal on deep abdominal inspiration. Via<sup>72</sup> reported normal but reduced excursion of the diaphragm on the affected side and normal excursion on the other side. Tardieu and Guilbert<sup>73</sup> mentioned that roentgen study in their case suggested eventration, but they did not mention movements of the leaflets of the diaphragm.

The cardiac shadow was invariably greater than normal in the right side of the chest in cases of eventration on the left side and was usually unchanged in cases of eventration on the right side. This observation is relatively constant both in cases of eventration and in cases of hernia and therefore offers no point in differentiation. In cases of eventration on the left side this change in the cardiac shadow to the right has many times been called dextrocardia. It is, however, not true dextrocardia. In cases of eventration the diaphragm is displaced superiorly, causing the heart not to be displaced to the right but rather to be pushed to the anterior thoracic wall with the end-result total displacement of the heart upward, rotation and elevation of the apex and curving of the aorta with broadening of the aortic shadow. The heart assumes the shape of an egg according to Dillon and becomes more and more aortic in form.

70. Ottosen: *Hospitaltid.* **67**:465 (July 23) 1924.

71. Botteri: *Gior. di clin. med.* **11**:1045 (Oct.) 1930.

72. Via: *J. de radiol. et d'électrol.* **16**:590 (Oct.) 1932.

73. Tardieu and Guilbert: *Bull. et mém. de la Soc. de méd. de Paris* **9**:310, 1931.

Other interesting associated roentgenologic observations have been reported. An esophagotracheal fistula in Lerche's case, hour-glass stomach in Verbrycke's fifth case and mild elevation or rudimentary eventration in Dillon's case add interest to the subject.

It has been reported several times that on inspiration the entire mediastinum moves to the side opposite the one affected. This was noted in 1 of our cases.

#### ELECTROCARDIOGRAPHIC OBSERVATIONS

A number of reports have been made regarding the electrocardiographic observations in cases of eventration. This study was undoubtedly done because of apparent dextrocardia. Baetge<sup>74</sup> probably made the first studies in 1913 and found certain departures from normal, but these have not been confirmed by subsequent reports. He stated that in lead 1 there was a negative Q wave which is not present in the normal electrocardiographic tracing. The P wave was shorter than normal but was not convergent, while the T wave was diphasic. In lead 2 the diphasic fluctuation was more pronounced, with first a negative, then a positive, wave. The greatest anomaly, according to Baetge's early study, appeared in lead 3. The T wave was again diphasic, the P wave was negative, and the Q and S waves were not pronounced. The R wave was lower and double-notched.

Siebeck<sup>75</sup> in discussing the heart in association with relaxed diaphragm mentioned the slowing of the heart and extrasystole, an observation which was confirmed by Labbé. Heudtlass, Maggi and Garre<sup>76</sup> after an electrocardiographic study reported sinus arrhythmia. Auricular fibrillation was present in 1 of our cases, but we feel that it was coincidental and not a result of eventration. Maher and Blackwood<sup>77</sup> in 1 case, Wood and Wood in 2 cases, Blackford and Booth in 1 case and Jewett in 1 case noted normal electrocardiographic tracings.

#### OTHER OBSERVATIONS

Korns in his résumé called particular attention to a sign based on the physiology of the diaphragm and cited the article by Hoover.<sup>78</sup>

74. Baetge: *Deutsches Arch. f. klin. Med.* **110**:49 (March) 1913.

75. Siebeck: *München. med. Wchnschr.* **79**:265, 1931.

76. Heudtlass, A. P.; Maggi, A., and Garre, O.: *Prensa méd. argent.* **20**:461 (March) 1933.

77. Maher, P. P., and Blackwood, J. D., Jr.: *U. S. Nav. M. Bull.* **30**:359 (July) 1932.

78. Hoover, C. F.: *Functions of the Diaphragm and Their Diagnostic Significance*, *Arch. Int. Med.* **12**:214 (Aug.) 1913; *Diagnostic Signs from the Scaleni, Intercostal Muscles and the Diaphragm in Lung Ventilation*, *ibid.* **20**:701 (Nov.) 1917; *Functions of Intercostal Muscles*, *J. A. M. A.* **73**:17 (July 5) 1919; *Am. J. M. Sc.* **159**:633 (May) 1920.

whose work on the diaphragm brought added knowledge of the function of this organ. In brief, he stated that unopposed by phrenic action the intercostal muscle will cause the entire costal margin to move away from the midline and that unopposed by the intercostal muscles the diaphragm will draw the entire margin toward the midline. The more nearly the curve of all or any part of the diaphragm approximates a plane, the greater mechanical advantage will that part of the diaphragm have in control of the costal margin to which it is attached. Therefore, the movement of the costal borders is a reliable index of elevation or depression of the diaphragm. The diaphragm and intercostal muscles are therefore antagonists. Normally the intercostal muscles are the stronger, and therefore on inspiration the costal margins throughout their whole extent move away from the midline. Korns made use of these facts and applied them to advantage in making a clinical diagnosis of eventration and in differentiating it from hernia. He stated that if one half of the diaphragm becomes accentuated without the formation of synechia between the thoracic wall and the phrenic leaf the result is an increase in the disparity between the resultant line of traction of the diaphragm and the curve of the diaphragm, and inspiratory divergence of the costal margin from the midline will be considerably in excess of that of the opposite normal side. Korns' remarks on this sign led Lord in 1927 to urge the use of these observations. Uspensky noted this observation in 4 of 5 cases and spoke of the phenomenon as Korns' sign.

Schlippe's procedure for measuring intragastric pressure has been mentioned by various authors. By inserting into the stomach a rubber tube to which is attached a rubber balloon which is blown up after the tube is in place and by connecting the space end with a measuring manometer and chest straps for simultaneously recording inspiration and expiration the relation between these and intragastric pressure can be observed and recorded. Normally intragastric pressure on an intact diaphragm would be increased on inspiration and decreased on expiration by pressure on the diaphragm from above. This relationship is maintained in cases of eventration of the diaphragm, but in cases of hernia of the diaphragm, in which the stomach invades the thorax through an opening in the leaf, no such pressure would be exercised and the reverse condition would be obtained. While in our first case this test was applied with the results that theoretically should be observed, many authors have condemned the method—some without using it in the conduct of their own cases.

The electric stimulation of the phrenic nerve has been suggested, and observation under the fluoroscope as to the extent of the excursion of the diaphragm has been carried out. Theoretically, if this test is applied to a normal person in the interim between respirations when other influencing factors of respiration are eliminated, it should result in a degree

of excursion directly proportional to the strength of the stimulus and the amount of normal conducting tissue in the phrenic nerve. If the phrenic nerve is paralyzed no resulting contraction takes place. Practically, reports in the literature indicate that this test is useless, as collateral stimulation of other muscles, like the scalene and intercostal muscles, and isolated effects on the diaphragm are by no means certain.

Pneumoperitoneum with subsequent fluoroscopy has been mentioned by many authors but the majority have felt that it is attended with danger, especially if done in the presence of a hernia of the diaphragm when air might enter the pleural cavity. Lord stated that it is not justified and mentioned gangrene of the stomach as a complication to the procedure. Overholt<sup>79</sup> agreed that it should not be done. Many authors mentioned it as a diagnostic procedure, but none seem to have attempted its use. Walton, for example, suggested pneumoperitoneum as the only diagnostic sign of any pathognomonic value, but he did not employ it in the study of his case. We gather from a study of the literature that this procedure has been a measure to write about but not to perform and, therefore, conclude that it should be eliminated from the modern diagnostic armamentarium. Dillon stated that Goetze and Schlecht and Wels recommended the procedure and that Freud and Horner in applying the method did not obtain satisfactory results because of adhesions in the abdominal cavity. In the case of Schlecht and Wels perforation of a gastric ulcer developed twenty-one days after pneumoperitoneum, and the patient died twenty-four hours after an operation.

#### DIAGNOSIS

It becomes evident from the foregoing material that a clinical diagnosis of eventration of the diaphragm even with the aid of all the available measures of precision is most difficult. Diagnosis from the physical signs is impossible, although Bayne-Jones stated that Janeway made a diagnosis on these signs alone. He further stated that this was the first instance of intravital diagnosis of the condition. One might suspect hernia, eventration or pneumothorax from the physical signs, but if the sign mentioned by Korns were constant one might definitely diagnose the condition. It is interesting to note that Kunkel<sup>80</sup> in presenting his case, the reproduced plates of which are very indistinct, said that "the combination of physical signs encountered is apparently pathognomonic of the pathology and if kept in mind similar cases may be recognized and properly certified to in many instances where X-Ray or post-mortem examination is not possible." This is somewhat contrary to the general thought, but on the other hand Dillon said that he was able to make a

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79. Overholt, R. H.: *Ann. Surg.* **91**:381 (March) 1930.

80. Kunkel, W. M.: *Pennsylvania M. J.* **33**:63 (Nov.) 1929.

correct diagnosis by clinical examination in 2 cases and that the diagnosis was later confirmed by fluoroscopic examination. Bamber suggested that in his case the condition should have been diagnosed "from the long history and the gurgling sounds so plainly heard in the chest posteriorly." To make a positive diagnosis on physical signs necessitates pathognomonic signs, and as there are none, in our opinion, one can only suspect the presence of eventration. Eggers said that he made a diagnosis of eventration after roentgenologic examination; the surgical preoperative diagnosis based on symptoms was hernia, the operative diagnosis was hernia and postmortem examination revealed localized eventration of the diaphragm. When such difficulties exist one must hesitate to make a positive diagnosis from physical and clinical signs alone.

A differential diagnosis of eventration must be made from hernia of the diaphragm, pleurisy with fluid, thickened pleura, thoracic stomach, pulmonary cysts, pulmonary tumors, atelectasis, emphysema and neurosis.

A differential diagnosis though at times fraught with difficulties is important whenever possible. Needless surgical procedures have not infrequently resulted from mistaken diagnosis. Exploratory thoracentesis and thoracotomy have been performed several times for fluid when eventration existed instead. Clopton's<sup>60</sup> case was a striking example of this fault in diagnosis. He reported the case of a baby 14 months old in whom a part of the eighth rib on the left side was removed and a tube was inserted for drainage. At the time the child had influenza and bronchopneumonia, followed by what was thought to be empyema. The drain remained in for six months, and a week after it was removed an abscess formed along the tract anterior to the fifth rib. When the child came under Clopton's observation the temperature was high, thirst was violent and vomiting was continuous. On the first roentgen study it was thought that diaphragmatic hernia existed, but later a diagnosis of eventration was made. Reexamination of the films taken at the time of the resection of the rib revealed the same condition. In Allan's case puncture was performed to drain off fluid. Levine mentioned that the stomach may be punctured by thoracentesis if eventration is mistaken for fluid. Thompson concluded in his case that pleural effusion existed and that the chest should be punctured, but the patient refused permission, and subsequent examination proved the objection a wise one as eventration was found. Morrison made a tentative diagnosis of pleural thickening in 1 of his cases, while Fatou and his associates suspected pleurisy at the first examination. Yater and Rodis<sup>61</sup> reported a case of pleural effusion in which eventration was suggested on roentgen study of the

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81. Yater, W. M., and Rodis, I.: *Am. J. Roentgenol.* 29:813 (June) 1933.



patient in a standing position, but this impression was readily cleared away when roentgen examination was made with the patient in the recumbent position.

Probably of all diseases from which eventration must be differentiated, hernia of the diaphragm is seen most frequently. The history of acute onset of symptoms following trauma leads some to favor the diagnosis of hernia. Others feel that the fluoroscopic study is all that is necessary for differentiation, but the two conditions remain at times difficult or impossible to differentiate.

Goodall and Hoyt<sup>82</sup> in a recent study and report on thoracic stomach present another differential problem which, while no such case has come under our observation, makes one feel that the roentgen study is readily and completely clarifying.

Levin and Cunningham and Shaw<sup>83</sup> and others have mentioned that eventration might incorrectly suggest a neurosis and that patients have symptoms resembling those of a neurotic person. We readily appreciate this, particularly when one reviews the detailed histories of some of the cases found in the literature. As in our first case, symptoms were bizarre and no clue was definitely suggested until after fluoroscopic study, although pleural effusion was considered after physical examination.

Exploratory operation has been suggested in preference to pneumoperitoneum, and while the latter is to be condemned, the former is a radical step to take to make a diagnosis and hardly seems justifiable.

In summary, the diagnosis of eventration of the diaphragm is difficult and rests with no one procedure unless Korns' application of the physiologic studies of the diaphragm becomes a universal sign.

#### PROGNOSIS

The prognosis of eventration is difficult to make and must therefore be guarded. In general, as far as life is concerned it is usually good, but it is, however, a disabling disease in many persons. In those cases in which there is true eventration, that is, congenital displacement, if severe symptoms do not arise in the first five years of life they usually do not make their appearance until the fourth decade or even much later. Quénu and Fatou felt that the benignity of eventration is exaggerated and that such patients are subject to more symptoms and complications than those with hernia of the diaphragm. Blackford and Booth, quoting a personal communication from R. Bartholomew, stated that the latter had a patient who was several months pregnant in whom elevation of

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82. Goodall, H. W., and Hoyt, L. H.: Thoracic Stomach, *Arch. Int. Med.* **53**: 549 (April) 1934.

83. Cunningham, L. W., and Shaw, W. M.: *J. Florida M. A.* **11**:7 (July) 1924.

the left side of the diaphragm was noted. Labor was precipitated, resulting in complete rupture of the diaphragm. It was concluded from this that eventration is a menace to young women of the child-bearing age.

#### TREATMENT

Medical management is the treatment of choice. Such therapy must inevitably be meager and entirely symptomatic. Wood and Wood tersely summarized management by saying that no curative treatment is possible. Absolute rest is essential, and while this may not necessarily be rest in bed, absence of physical exertion is essential. The relief of gastro-intestinal symptoms such as gas, bloating, fulness, nausea and vomiting, which are often distressing, is urgent. The use of the usual intestinal antispasmodics and a bland, nonirritating diet with a low residue may at times add to the comfort of the patient. Lord in the report of his first case stated that rest in bed always improved this particular patient. Many patients were found to be overweight, a condition which should be corrected. Sedatives are at times imperative, and we believe that bromides in amounts sufficient to produce physiologic effects are of much value, while the barbiturates are the next choice, and only occasionally are morphine and allied drugs resorted to for relief of distress. The treatment of associated diseases is not to be overlooked or neglected. Dillon's exhaustive study on the subject contained but a few lines on therapy and in summary said that hygienic and dietetic measures are the only reliable means of relief.

Surgical intervention in cases of eventration has been done a number of times but has not proved to be a marked success. Quénu and Fatou in a splendid report said that in all literature one finds the statement that hernia is operable and eventration is not, and they determined to disprove this idea. Careful search of the literature on the subject of surgical intervention in the presence of eventration may be summarized in the following outline:

	No. of Cases
Operations directly on the diaphragm for cure or relief.....	4
Exploratory operations.....	14
Operations for the coexisting disease.....	14

*Operations on the Diaphragm.*—This means surgical procedures on the diaphragm with the intention of correcting the pathologic condition present.

1. Lerche, through an abdominal incision, plicated the diaphragm in a woman, aged 38, who had also an esophagotracheal fistula. He made a final report <sup>84</sup> with

84. Lerche, W.: Infected Mediastinal Lymph Nodes as Source of Mediastinitis, Arch. Surg. 14:285 (Jan., pt. 2) 1927.

necropsy observations five years after the original operation. There was no trace of the phrenoplication; the affected leaf had been held in its place since the operation, and the patient had thereby been relieved of distressing symptoms.

2. Fatou and Lafourcade<sup>85</sup> reported a case in 1922 which Fatou again reported in 1928<sup>30</sup> in which a man 44 years old complaining of gastric distress with emaciation was operated on through an abdominal incision. All the organs under the diaphragm were pulled down, the spleen was removed and the incision was closed. Immediately a thoracic incision in the seventh interspace was made, the ribs were separated and plication of the diaphragm from above was done. Three days later the patient died. Necropsy revealed that the plication had not held.

3. In Morrison's case a girl aged 10 was operated on by the thoracic route only. The diaphragm was found to be thinned out and of dense fibrous tissue. Partial excision of the diaphragmatic sac was done, followed by an uneventful convalescence. An examination three years later revealed the "bowline" not as high as before, the movements of the diaphragm free but reversed and no symptoms.

4. Quénu and Fatou reported their case in which a pneumothorax was done first, with a second stage consisting of a thoracolaparotomy beginning in the sixth interspace with resection of the costal cartilage. One hand was introduced, and the abdominal organs were pulled down. The diaphragm was then plicated on its convex surface. Roentgenographic study after the operation revealed the diaphragm 8 inches (5.08 cm.) lower, and two and one-half months later there were no symptoms.

*Exploratory Operations Not Directly on Diaphragm.*—1. Fischer in 1914 did a thoracotomy on a patient convalescing from pneumonia and typhoid fever, but finally made a diagnosis of eventration. The authenticity of the diagnosis of this case was questioned by Korns.

2. Bouquet, Masselot and Jaubert de Beaujeu in 1921 made a diagnosis of diaphragmatic hernia. Thoracotomy revealed no hernia; at necropsy eventration was found.

3. In Clopton's case, which was mentioned previously, thoracotomy and resection of a rib was done because eventration was mistaken for pleural effusion.

4. Glaser's patient was operated on by Korte in 1903. An exploratory laparotomy was done for hernia, but eventration was found. The abdomen was closed with no further surgical procedure.

5. Roux in 1915 made a preoperative diagnosis of hernia of the diaphragm, but eventration was found on exploratory operation, so no further surgical steps were taken.

6. Schlecht and Wels<sup>86</sup> confirmed their diagnosis by exploratory operation, but no corrective procedure was attempted.

7. Robineau and Quénu in 1919 performed a thoracolaparotomy on a patient of Louste and Fatou. The preoperative diagnosis was hernia of the diaphragm, but pleuroperitoneal tuberculosis with caseous masses was found at operation. The wound was immediately closed; necropsy disclosed eventration.

8. Bayne-Jones' patient was operated on by Phinney for disease of the gallbladder. On exploration the gallbladder was found to be normal, but eventration

85. Fatou and Lafourcade: Bull. et mém. Soc. méd. d. hôp. de Paris 46:505, 1922.

86. Schlecht and Wels: Fortschr. a. d. Geb. d. Röntgenstrahlen 27:544, 1920.

of the right side of the diaphragm was disclosed, for which nothing was done. The patient died ten days later.

9. Verbrycke's first patient was operated on by C. S. White in 1914. The colon was freed, but no further repair was attempted. Three years later the symptoms were improved.

10. Madinaveitra<sup>37</sup> reported the case of a patient who was operated on for cancer of the stomach which did not exist; eventration was found, but no further surgical intervention was done.

11. Jawara and Dumitresco-Mante did an exploratory laparotomy subsequent to puncture of the base of the right lung at which time fluid was obtained. A hydatid cyst was found under an elevated diaphragm. Two years later the patient was well.

12. In Egger's case a preoperative diagnosis of hernia of the diaphragm was made. A simple laparotomy was done with no repair of the diaphragm. The child died fourteen hours after the operation; necropsy revealed eventration.

13. Heidenreich<sup>87</sup> reported a case in which an exploratory laparotomy was done and a gastric volvulus and eventration were found.

14. Our first case, which is reported later, falls into this group.

*Operation for Coexisting or Associated Disease.*—1. Baetge's case in 1913 was one of cholelithiasis in a man aged 28. Eventration of the diaphragm was found on operation.

2. Sicilliano reported a case of pyloric obstruction due to cancer. At operation this condition was confirmed and eventration was found. A gastro-enterostomy was done.

3. Kienböck's<sup>88</sup> patient was operated on to relieve an obstruction of the pylorus due to ulcer, at which time the diagnosis of eventration was confirmed.

4, 5 and 6. Boughert (de Lyon), cited by Quénu and Fatou,<sup>29</sup> operated on 3 patients with ulcer on the lesser curvature of the stomach coexisting with eventration. In 1 a partial gastrectomy was done, in 1, a Balfour operation with a gastro-enterostomy four months later, and in 1, a gastro-enterostomy.

7. Berg in 1917 resected 3 feet (91.4 cm.) of colon in a case of megacolon associated with eventration on the right side. This was the case of Aronson,<sup>89</sup> of which Korns said that if eventration was confirmed at operation "the author's vague description of the findings raises much doubt."

8. Quénu cited the case of Carnot in which a total colectomy was done for the relief of megacolon. Eventration of the diaphragm was found, but no direct attack was made on this pathologic condition. The patient died the next day.

9. Wood and Wood reported the case of a man 68 years of age whose health had been good, and he had worked for forty-five years without losing a day. An intestinal obstruction developed. About one week after the operation a high diaphragm was noted.

10. Verbrycke's second patient was operated on for perforated gastric ulcer high on the lesser curvature of the stomach, at which time many adhesions and an eventration of the diaphragm were found. Verbrycke stated that three weeks later

87. Heidenreich: *Prensa méd. argent.* **19**:792 (Oct.) 1932.

88. Kienböck: *Fortschr. a. d. Geb. d. Röntgenstrahlen* **21**:322, 1914.

89. Aronson, E. A.: *New York M. J.* **108**:196, 1918; *M. Rec.* **93**:37, 1918.

the stomach was functioning normally and the diaphragm was somewhat lower. Roentgenograms taken four months later showed the diaphragm to be 4 inches (121.9 cm.) lower. This and the first case that this author reported seem to be the only 2 on record in which the position of the diaphragm was improved by the correction of associated conditions, as confirmed by roentgen study.

11. In Morrison's case the patient was operated on for pyloric obstruction due to torsion of the stomach, at which time eventration was found.

12. Golob's patient showed a "growth at the cardia" on esophagoscopic examination. Lilienthal performed this operation and found a carcinoma at the cardiac end of the stomach and the right side of the diaphragm elevated high in the chest.

13. Foster's patient was a girl aged 14 years who had previously been healthy and now complained of pain in the lower portion of the abdomen. At operation a large ovarian cyst was found and removed. A search for the appendix disclosed an abnormal position of the transverse colon. Subsequent roentgen study revealed a high diaphragm and the cecum above the liver.

14. In Allan's case puncture was done for the treatment of pleural effusion on the left side, which was not present. Eventration was found on subsequent study.

This review of surgical management of eventration or surgical intervention in associated conditions leaves one with the impression that such treatment offers little hope for a cure.

#### REPORT OF CASES

CASE 1.—*History*.—B. T. H., a fireman, was a married man aged 45, the father of two children. His chief complaint was choking spells and fainting with shortness of breath and pain in the lower anterior part of chest.

The onset of the symptoms was rather gradual, although the patient dated their beginning from an accident (this accident was believed to have been preconceived to gain compensation). However, the symptoms had been present for about nine years. The patient met with an accident in October 1924 when he was thrown from a fire-truck, striking the lower anterior part of the chest against an object and being rendered semiconscious. He likewise sustained a fracture of the left humerus and left wrist. The first symptoms noted were an ache in the left upper extremity extending into the back of the neck and numbness of the fourth and fifth fingers of the left hand which appeared white when the patient arose in the morning and were so stiff that he could barely move them. Since that time he had had an attack of weakness two and three times a day. These attacks consisted of cold sweats, weakness in the knees, sensation of cold and warmth, gasping for breath and the impression that consciousness was leaving him. He felt that there was pressure against the heart. Dyspnea appeared after the accident and had gradually grown worse, being exaggerated on exertion, with palpitation of the heart. The cough which occurred with attacks of dyspnea was unproductive. There was pain in the lower anterior portion of the chest on the left on deep breathing, exertion or emotional excitement. Nervousness was apparent.

*Family History*: The patient's father died at the age of 64 of an unknown cause. The mother, aged 69, two brothers, aged 52 and 37, and four sisters aged 50, 48, 40 and 38, respectively, were living and well. No chronic diseases were known to have existed in the family. Three sisters died in infancy.

*Previous Personal History*: No childhood diseases were known. The patient had an occasional cold. His tonsils were removed in 1913. He had had no major

illness up to the time of the accident. In the previous twelve years the official record of the department in which he worked showed only minor illness such as cough, grip and minor infections; there was no special mention of severe symptoms suggesting thoracic or gastro-intestinal disease.

*Physical Examination.*—The pulse was 92, the temperature, 98 F., the respiratory rate, 24, and the blood pressure, 144 systolic and 90 diastolic. The pulse was irregular in rhythm and volume. Many teeth were missing; the remainder appeared normal. The tongue was clean. The tonsils had been removed. The gag reflex was increased. The pupils reacted to light and in accommodation. The thyroid gland was normal. There was no general adenopathy. The nasal accessory sinuses and the mastoid were clear.

The chest was of the asthenic type. Expansion was free and apparently equal. The right lung was apparently normal. On the left side anteriorly there was a tympanitic note from the fourth rib distally. Laterally and posteriorly in the

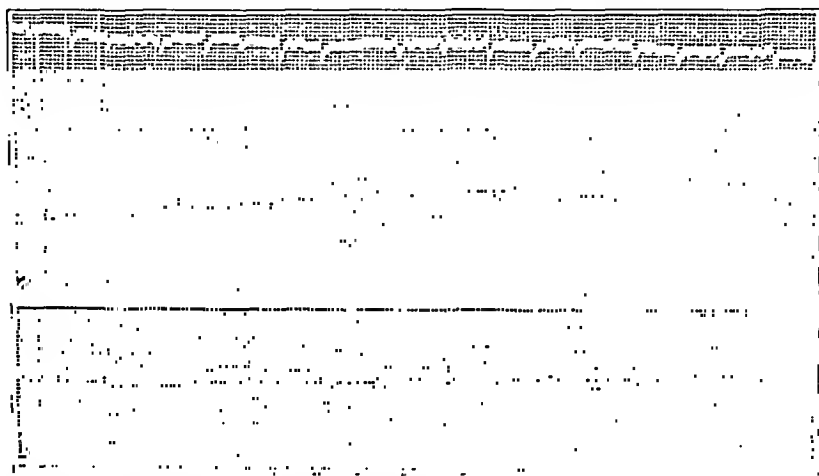


Fig. 1 (case 1).—The electrocardiographic tracing which confirmed the impression of auricular fibrillation with myocardial damage.

axillary line was an area of dullness from the angle of the scapula down to the base of the lung. Anteriorly there was a gastric tinkle over the fifth interspace. Over the entire left lung in the lower half anteriorly and posteriorly were diminished breath sounds and voice sounds. No râles were noted. Examination for Hoover's or Korns' observation was made after roentgen examination. Measurements of the chest movements including those of the subcostal angle were not indicative of any difference in the two sides, although the patient was rather obese and accurate measurements might not have been obtainable. Examination of the heart revealed that the apex was not visible or palpable. There was no bulging of the precordium and no thrills. The left border extended 9 cm. to the left of the midsternal line in the fifth interspace and 6.5 cm. to the right of the midsternal line. There was a definite disorderly irregularity suggesting auricular fibrillation. The heart sounds were of poor quality and intensity. The apex beat was faster than that of the pulse.

The abdomen was well rounded with considerable subcutaneous fat. The liver, spleen and kidneys were apparently normal. There was no local or general tenderness or rigidity and no masses. All the superficial and deep reflexes were normal. The extremities were normal. Urinalysis gave normal results.

*Examination of the Blood.*—The white cell count was 9,150, the red cell count was 5,000,000, and the hemoglobin content was 93 per cent. The differential count was: band forms, 3 per cent; segmented forms, 63 per cent; eosinophils, 2 per cent; monocytes, 2 per cent, and large and small lymphocytes, 31 per cent.

*Electrocardiographic Study.*—The ventricular rate was 140 with irregular rhythm. The P wave was replaced by fibrillary waves. The QRS complex occupied 0.08 second and was upright and slurred in leads 1 and 2, inverted and



Fig. 2 (case 1).—A roentgenogram of the chest showing the curved unbroken bowline with the air-filled stomach below.

split in lead 3 and of low voltage throughout. The T wave appeared to be inverted in lead 1 and upright in leads 2 and 3; they were of low voltage throughout. The diagnosis was auricular fibrillation with myocardial damage.

*Roentgen Study.*—Several examinations were made in a short period of time by different roentgenologists.

The first examination was made by Dr. A. B. Moore and Dr. E. M. McPeak. Fluoroscopic examination of the chest revealed marked elevation of the diaphragm on the left. Examination of the esophagus and stomach revealed the stomach high on the left side although apparently below the diaphragm. The roentgenologist believed that this was the result of eventration of the diaphragm, although the possibility of hernia could not be entirely excluded. Apparently the colon was very high on the left side. Further examination was made a week later. The

ribs on the left side showed no definite evidence of injury. The diaphragm was markedly elevated. The stomach was situated high on the left side but was definitely beneath the dome of the diaphragm.

The second examination was made about two weeks later by Dr. Claude Moore who made the following report: The patient was examined under the fluoroscope in the sitting position because he was too weak to stand. There was marked elevation of the diaphragm on the left side with decrease in the chest space on the left and compensatory dilatation of the right side of the chest. There was rather extreme motion of the diaphragm on the right. The heart was displaced to the right so that the center of the heart was about in the midline. The diaphragm on the left was fixed and reached to the level of the third interspace anteriorly

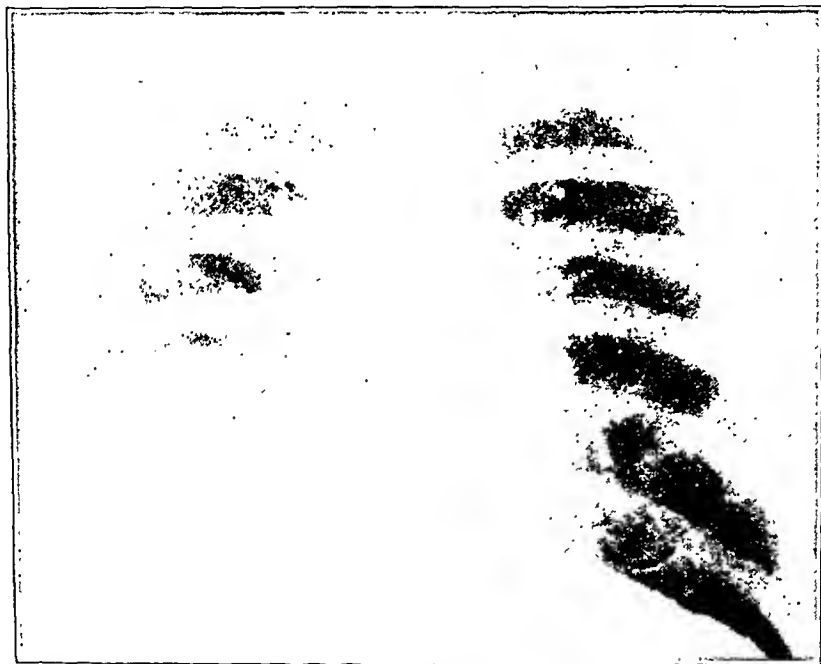


Fig. 3 (case 1).—A roentgenogram showing the high diaphragm and the stomach below apparently filled with fluid.

and to the level of the seventh interspace posteriorly. Respiratory motion showed paradoxical motion of the diaphragm on the left. In other words, as the diaphragm went down on the right side it went up on the left side, and the mediastinum was pulled to the right. There was considerable gas in the stomach, and the left border of the heart could be seen through the gas. The upper walls of the stomach and diaphragm on the left side were from two to three times average normal thickness. The impression was that the condition was the result of an old respiratory process, either of inflammation or of injury. If it were the result of a congenital condition or of paralysis of the left phrenic nerve the diaphragm would have been markedly thinned out. The diagnosis was marked elevation of the diaphragm on the left side with paradoxical motion on respiration.

*Operation and Surgical Notes.*—A Mayo-Robson incision on the left side permitted exploration of the abdomen and the left side of the thoracic cavity. The



diaphragm on the left was tense and at the height of the fourth rib. The stomach, large and small intestine, omentum and spleen were in the thoracic space. The viscera were dislodged with difficulty and placed in the abdominal cavity, and the wound was closed.

Exploration revealed the following: 1. The diaphragm was displaced to the level of the fourth rib and was tense at all times during both inspiration and expira-

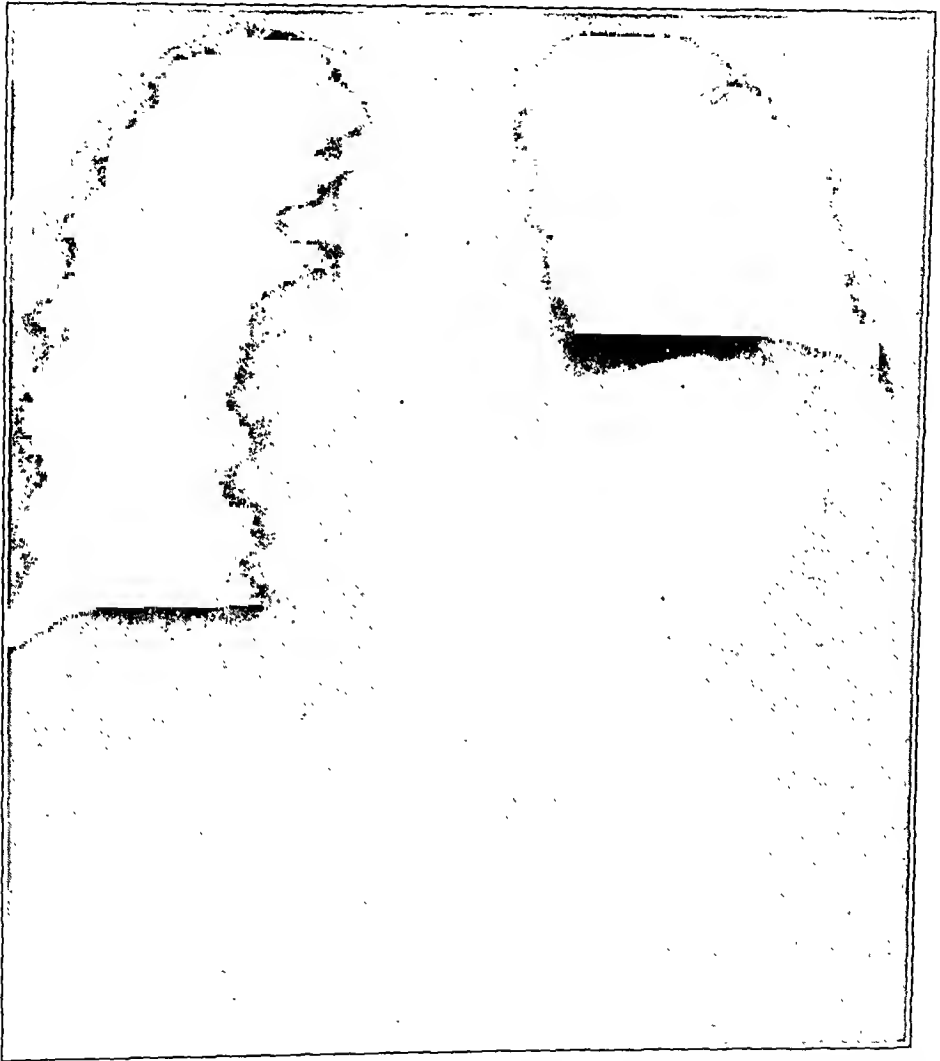


Fig. 4 (case 1).—A roentgenogram of the stomach filled with barium below the elevated diaphragm. The heart shadow is to the right.

tion. 2. The mediastinum containing the heart was bulging into the cavity of the chest. The diaphragm was so thin as not to be recognized, and the impression was that the heart was exposed and covered only by the pericardium. 3. The ribs surrounding the wall of the chest were superficial, with the thinnest possible covering that could hardly be recognized as tissue of the diaphragm. 4. Over the anterior lower border of the chest was a curtain of tissue suggestive of a former diaphragmatic attachment.

The opinion was that in order to repair the diaphragmatic defect it would have been necessary to open the wall of the chest anteriorly up to the third rib. Having accomplished this it did not appear possible or plausible to place stitches that would hold in the presence of a thinned out lateral diaphragmatic wall. It seemed unjustifiable to subject the patient to grave risk with little hope of accomplishing any good.

CASE 2.—*History*.—E. H. H., a married man aged 42, a policeman, was shot accidentally while cleaning a pistol. The bullet pierced the anterior wall of the chest to the left of, and just below, the left nipple and made its exit posteriorly

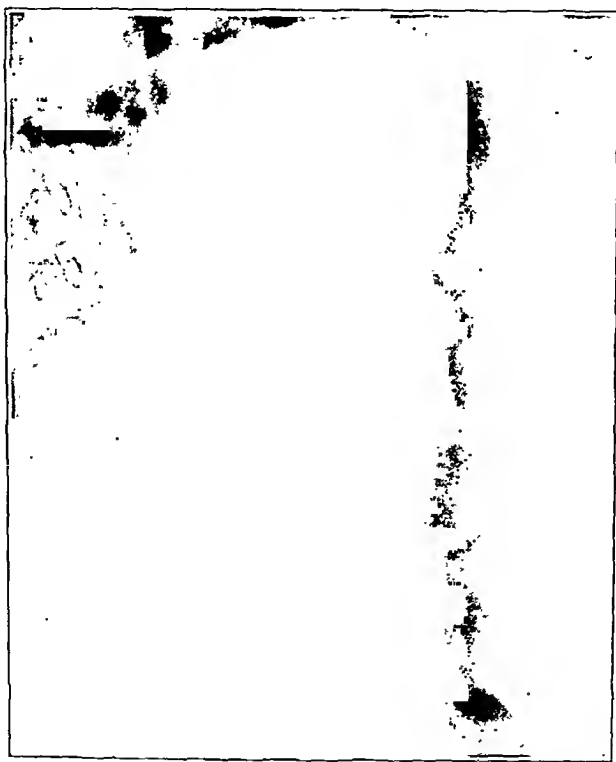


Fig. 5 (case 1).—A lateral view showing the high diaphragm and the stomach filled with barium.

immediately below the angle of the scapula. He was taken immediately to the emergency room of the Garfield Memorial Hospital. The pulse was weak and rapid, and the patient was in a state of severe shock. Morphine sulphate was given subcutaneously with physiologic solution of sodium chloride. The patient remained in the hospital eighteen days, and then was taken home in an ambulance. He returned to work about two months later, apparently cured. Physical examination during his stay in the hospital revealed a normal condition with the following exceptions: The blood pressure on admission was 48 systolic and 32 diastolic, rising to 80 systolic and 70 diastolic in the course of six hours after emergency treatment. There was evidence of anemia and shock, and a few scattered bubbling

râles were heard over the anterior lower portion of the chest on the left near the site of the wound. Two days later effusion of the left pleural cavity developed. There were some coughing of blood and pain in the chest with nausea, restlessness and fever until the patient was discharged. The diagnosis was gunshot wound of the chest with injury to the pericardium and subsequent pleural effusion. Two and one-half months later a fluoroscopic examination revealed the diaphragm on the left to be quite high and a large gas bubble of the stomach immediately below. At this time we were unable to determine definitely whether the shadow was of the diaphragm or of a possible fluid level. Subsequently a roentgen examination was made.

The previous and familial history was irrelevant.

*Physical Examination.*—The blood pressure was 120 systolic and 80 diastolic. The heart gave no evidence of displacement, enlargement, murmurs or arrhythmia.



Fig. 6 (case 2).—A roentgenogram of the chest showing the curved, unbroken bowline with the air-filled stomach. Thickening of the interlobar pleura is evident.

The sounds were slightly distant. The right lung was normal in every respect both anteriorly and posteriorly. Percussion over the left lung revealed diminished sounds not heard in the lower third of the chest anteriorly and posteriorly. There were diminished breath sounds on the left over the dull area but no râles. No gastric tinkle or gurgle was heard, and there was no tympanitic note over the anterior lower portion of the chest on the left. There seemed to be a lag on the left side. There was no Korns' sign. The remainder of the physical examination gave normal results.

*Roentgen Examination.*—Examination on the day of admission to the hospital revealed complete opacity of the entire left side of the chest with displacement of the heart and great vessels to the right. The trachea was also markedly displaced to the right. The opacity was evidently due to hemorrhage.

Examination on the fifth day of hospitalization revealed opacity of the entire left side of the chest with displacement of the heart and great vessels to the right. The opacity appeared to be caused by fluid.

Fluoroscopic examination in the upright position on the eighth day of hospitalization revealed no evidence of pneumothorax. Uniform opacity of the entire left side of the chest suggested the presence of fluid.

Examination on the day of discharge revealed the exudate in the left side of the chest to be materially decreased over the previous examinations. The upper third of the left lung was pneumatic.

Examination was made six weeks after discharge from the hospital. Posteriorly and anteriorly the chest showed evidence of an irregular area of increased density in the region of the base of the left lung where there was also suggestive evidence of some insistent air. The observations were compatible with a diagnosis of

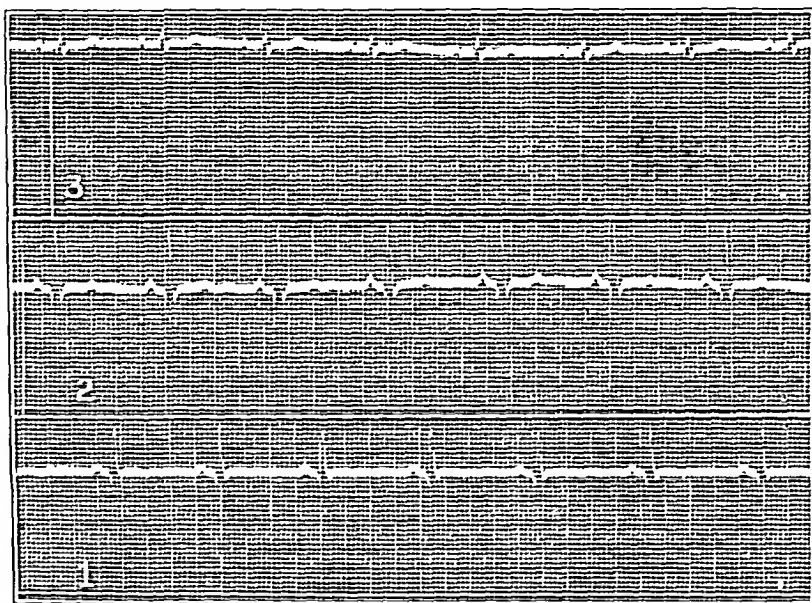


Fig. 7 (case 2).—The electrocardiographic tracing which confirmed the impression of myocardial damage.

pleural effusion of moderate degree with a small pneumothorax and some pneumonitis, but the possibility of herniation of the diaphragm was considered. A fluoroscopic examination was recommended. The apex of the left lung and the entire right lung were relatively clear. The heart was of normal size and shape but was displaced slightly to the right.

Examination by another roentgenologist ten weeks after discharge from the hospital revealed a rather marked elevation of the diaphragm on the left with thickening of the pleura over it. Fluoroscopically there was no evidence of movement of the diaphragm on this side. The diaphragm on the right side appeared to be normal.

*Electrocardiographic Study.*—The conclusion was that there was evidence of mild myocardial damage.

*Summary.*—The patient had a gunshot wound of left side of the chest with subsequent pleural effusion. The effusion cleared up, and later eventration of the diaphragm was found, probably caused by injury or section of the phrenic nerve.

#### SUMMARY

A complete résumé of eventration of the diaphragm was given with a study of the literature and the addition of 2 new cases.

# ACUTE APPENDICITIS IN DOGS

## AN EXPERIMENTAL STUDY

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AND

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MADISON, WIS.

Stimulated by a desire to compare the conservative and operative methods of treating acute appendicitis, we undertook to produce acute appendicitis in dogs.

Anatomically the dog has no appendix, but the cecum, which is blind, serves as an admirable substitute. The terminal portion of the ileum joins the cecum at its junction with the ascending colon. The lesion of acute appendicitis was produced in varying degrees of severity by ligation of one, two or three of the arterial branches supplying the organ, by crushing and ligating the base of the organ or by a combination of these methods.

## EXPERIMENTAL METHODS

Table 1 shows the general plan of the experiment. Appendical damage of mild, moderate or severe degree was produced, and the dogs which survived were examined at intervals thereafter of one, two or three months. Essentially equal numbers of dogs with each degree of damage were examined after operative or conservative treatment. Of the forty-eight dogs in the series twenty-eight survived, fifteen of which were given conservative treatment while thirteen were operated on. The mortality among the dogs with mild appendical damage was 12.5 per cent; among those with moderate damage, 52 per cent, and among those with severe damage, 80 per cent, the total average mortality being 42 per cent.

Conservative treatment after laparotomy to produce the lesion consisted of the daily administration subcutaneously of physiologic solution of sodium chloride and intravenously of a solution of 5 per cent dextrose, usually in doses of 500 and 200 cc., respectively. Morphine was given freely to keep the dogs quiet.

Nothing was given by mouth, and the parenteral fluids were administered until the animal showed a desire for water. The diet was then gradually increased according to the clinical course.

Operative treatment after a laparotomy to produce the lesion began with a second laparotomy from twenty-four to forty-eight hours later. This was done preferably through a second incision (the first operation in the later experiments was through a left rectus and the second operation through a right rectus incision), and drainage of the area around the appendix was instituted with a soft rubber Penrose drain filled with gauze. The inflammatory lesion was disturbed as little as possible, and the drain was sutured in place. The abdomen was closed entirely

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with interrupted stitches in layers. Parenteral fluids were administered as to the animals given conservative treatment. Subsequently reexamination of the dogs was made after one, two or three month intervals, as in the case of those treated conservatively. Table 1, for example, shows that only one of the dogs operated on with severe damage survived. Four other dogs so treated died. The degree of damage was estimated by the measures taken to produce the lesion and careful consideration of the clinical result produced.

## RESULTS

Table 2 gives a comparison of the mortality among the dogs treated conservatively and those treated by operation grouped according to the

TABLE 1.—*Summary of Experiment in Twenty-Eight Dogs*

Degree of Damage	Reexamination of 15 Dogs Treated Conservatively			Reexamination of 13 Dogs Treated by Operation			Results		
	1 Mo.	2 mo.	3 mo.	1 mo.	2 mo.	3 mo.	Well	Dead	Mortality, Percentage
Mild.....	2	2	4	2	2	2	14	2	12.5
Moderate...	2	2	3	2	2	2	13	14	52.0
Severe.....	..	..	..	..	..	1	1	4	80.0
Total.....	4	4	7	4	4	5	28	20	42.0

TABLE 2.—*Mortality According to Severity of the Lesion*

Degree of Damage	Number of Dogs	Result		Group Conservatively Treated		Group Operated on	
		Well	Dead	Dead	Mortality, Percentage	Dead	Mortality, Percentage
Mild.....	16	14	2	0	0	2	33.3
Moderate.....	27	13	14	5	42	9	60
Severe.....	5	1	4	1	100*	3	75
Total.....	48	28	20	6	29	14	52

\* Only one dog with severe damage was treated conservatively.

severity of the lesion. In the group with mild damage there was no mortality among those which received conservative treatment, but a mortality of 33.3 per cent among those operated on. In the group with moderate damage a mortality of 42 per cent followed conservative treatment and a mortality of 60 per cent followed surgical treatment. In the group with severe damage the mortality was 100 per cent following conservative treatment and 75 per cent following operation. It should be stated that only one animal with severe damage received conservative treatment, whereas four dogs with severe damage were operated on. Total mortality following conservative treatment was 29 per cent and following surgical treatment, 52 per cent. It is only fair to

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state that evisceration is more likely to occur in dogs than in man and that this complication caused two of the fourteen deaths following operative treatment.



Fig. 1.—General adhesions after appendicitis produced experimentally.

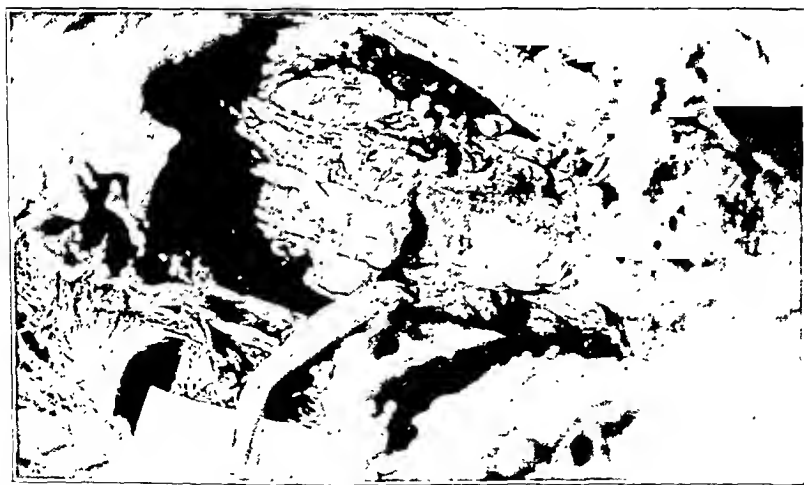


Fig. 2.—Generalized peritonitis in a dog which died after drainage. The drainage tube, drainage tract and generalized peritonitis are shown.

The causes of death are grouped in table 3 which shows 65 per cent of the fatalities to be due to generalized peritonitis. A mortality of 10 per cent was noted in each group with gangrenous appendicitis with



localized abscess, volvulus and evisceration. One dog with gangrenous appendicitis died under anesthesia. The two types of treatment are again compared. The most outstanding finding is a mortality of 23 per cent following conservative treatment of generalized peritonitis in comparison with a mortality of 77 per cent in the group operated on. The total mortality in the series was 30 per cent for the group treated conservatively and 70 per cent for those treated by operation.

Aside from the mortality alone, the observations were of interest because of postoperative conditions, notably adhesions. Table 4 shows

TABLE 3.—*Causes of Death Following Experimental Appendicitis*

Cause	Total		Conservative Treatment		Operative Treatment	
	Number	Percentage	Number	Percentage	Number	Percentage
Generalized peritonitis.....	13	65	3	23	10	77
Gangrenous appendicitis with localized abscess.....	2	10	2	100	..	..
Volvulus.....	2	10	1	50	1	50
Evisceration.....	2	10	..	..	2	100
Gangrenous appendicitis plus anesthesia.....	1	5	..	..	1	100
Total.....	20	100	6	30	14	70

TABLE 4.—*Grade of Adhesions Found Following Experimental Appendicitis*

Degree of Damage	Reexamination of Group Treated Conservatively				Reexamination of Group Operated on			
	1 mo.	2 mo.	3 mo.	Percentage 46.7	1 mo.	2 mo.	3 mo.	Percentage 100
Mild.....	1, 1*	0, 1	0, 0, 1, 1	63	2, 2	1, 3	2, 3	100
Moderate.....	1, 1	0, 0	0, 0, 1	43	3, 3	3, 3	3, 3	100
Severe.....	....	....	....	..	....	....	3	100

\* 0 means no adhesions, 1 means mild adhesions, 2 means moderate adhesions and 3 means severe adhesions.

the grade of adhesions found in each of the twenty-eight dogs which survived, grouped according to the degree of appendical damage produced. For example, according to table 4, four dogs with a mild degree of damage which were conservatively treated were reexamined after three months. Two of these showed no adhesions and two more showed mild adhesions. Similarly, of two dogs with mild damage treated by operation and examined again after three months, one dog had moderate adhesions and one, severe adhesions. The striking fact brought out in this table is that less than one half of the dogs treated conservatively had peritoneal adhesions except over the surface of the appendix itself, whereas 100 per cent of those which underwent surgical intervention were found after various intervals to have adhesions. In all

the dogs but one the adhesions were of at least moderate degree, and nine of thirteen dogs showed severe adhesions.



Fig. 3.—Generalized peritonitis in a dog which died, showing the cavity of an appendical abscess.



Fig. 4.—A single fine adhesion from the omentum to the under surface of the abdominal scar. The appendix and peritoneum elsewhere were entirely without adhesions.

While we realize that human beings and dogs are different, there are certain features which are similar. Infection, no matter whether in dog or in man, has three factors which determine the outcome of the

process, namely, dosage, virulence and resistance. These factors may be influenced individually or collectively. The introduction of an anesthetic and an operation reduce the resistance both locally and generally and enhance the virulence. The dosage is important. However, with surgical intervention the damage done to the resistance of the patient is greater than the beneficial results obtained by decreasing the dosage. Therefore, we feel that the patient has a better prognosis if there is no operation. This we have demonstrated experimentally and clinically, and it is in accord with fundamental principles of bacteriology.

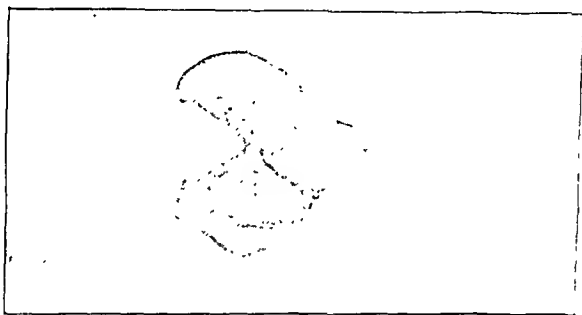


Fig. 5.—An appendix with one small omental adhesion to its base.



Fig. 6.—A typical coiled appendix without adhesions three months after appendicitis had been produced experimentally.

#### CONCLUSIONS

We believe that the following definite deductions can be drawn:

1. The cause of death in the majority of cases of acute appendicitis is generalized peritonitis, and conservative treatment causes a lower mortality than operative treatment (29 per cent conservative; 52 per cent operative).

2. Adhesions in the peritoneal cavity are distinctly increased by operative procedure and drainage (more than doubled in our experiment).



## EXPERIMENTAL BURNS

### I. THE RATE OF FLUID SHIFT AND ITS RELATION TO THE ONSET OF SHOCK IN SEVERE BURNS

HENRY N. HARKINS, M.D.

CHICAGO

There is still much diversity of opinion as to the mechanism of production of the clinical picture in the early stages of heat burns. Wilson<sup>1</sup> divided the effects of severe burns into four stages: (1) primary shock, (2) secondary shock, (3) septic toxemia and (4) healing. There is considerable difference in the way various authors define primary shock; some separate it from secondary shock by the time factor and others by the difference in the causative mechanism.

Using a time definition, Blalock<sup>2</sup> stated:

Primary shock, or collapse, refers to the condition in which a decline in the blood pressure and the appearance of the symptoms of shock are noted immediately following the injury. In secondary shock, the time interval separating the injury and the appearance of symptoms is usually an hour or more. In some instances primary shock may progress into the secondary type.

Wilson stated:

Initial shock is of nervous origin, is similar in nature to fainting or syncope, but longer in duration, and is due to a primary disturbance of the vasomotor mechanism. . . . It arises immediately after the injury and in the majority of cases is transient and slight in degree, and is rarely of serious significance.

Using this interpretation of primary shock, Wilson found that only 2.5 per cent of eighty fatalities from burns occurred at this stage. It is to be realized that primary shock may be present in many cases and yet not be the cause of death. Robertson and Boyd<sup>3</sup> used a much looser definition of primary shock, including changes found up to twenty-four hours after burning. They stated: "Death from burning occurring within the first twenty-four hours is practically always due to primary shock." This accounts for the high percentage of deaths in the first stage in their cases, namely, 41 per cent of thirty-two deaths.

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From the Douglas Smith Foundation, and the service of Dr. Edmund Andrews, Department of Surgery, University of Chicago.

\*1. Wilson, W. C.: Treatment of Burns and Scalds by Tannic Acid, *Brit. M. J.* 2:91 (July 21) 1928.

\*2. Blalock, Alfred: Acute Circulatory Failure as Exemplified by Shock and Hemorrhage, *Surg., Gynec. & Obst.* 58:551 (March) 1934.

\*3. Robertson, Bruce, and Boyd, Gladys: Toxemia of Severe Superficial Burns in Children, *Am. J. Dis. Child.* 25:163 (Feb.) 1923.

From the experimental standpoint it is possible that not all the features of primary shock may be shown in a completely anesthetized animal. Psychogenic factors are obviously nonexistent, and neurogenic influences are not completely comparable to those in conscious human beings. However, Blalock<sup>4</sup> was able to produce a picture simulating neurogenic primary shock by striking the abdomens of anesthetized dogs with a flat board. It is possible that the effects produced in cases of burns are due to widespread damage to numerous nerve endings in the skin (Wilson) giving rise to vasodilatation reflexly through centers in the medulla. There is, however, no good experimental evidence that such a condition as primary shock exists in the case of burns. Johnson and Blalock<sup>5</sup> found that the blood pressure of dogs rose in some cases, although it usually fell during the process of burning. In three experiments reported later in the present article the blood pressure taken during burning was as follows: In experiment 5 it rose from 114 to 146 mm. of mercury; in experiment 6 it rose from 120 to 160 mm., and in experiment 8 it fell from 132 to 116 mm. Underhill and Kapsinow<sup>6</sup> stated that primary shock never exists in anesthetized animals unless some part of the central nervous system has been subjected to the heat.

The third stage of the effects of severe burns is more a problem of secondary infection and not a direct result of the burn itself. Only 2.5 per cent of the eighty fatalities in Wilson's cases of burns occurred in this stage. Patients in the fourth or healing stage come under the province of the plastic surgeon. It is chiefly with the second stage of burns, the period of secondary shock, that the present paper has to deal. Eighty per cent of the deaths in Wilson's cases occurred in this stage.

#### SECONDARY SHOCK FOLLOWING BURNS

Secondary shock following burns is similar to secondary traumatic shock following other types of injury. It was not until the general problem of traumatic shock was elucidated that a clear conception of the pathologic physiology of burns was obtained. A quotation from Phemister's<sup>7</sup> article in 1928 is the first recorded statement based on

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4. Blalock, Alfred: Effects of Primary Shock on Cardiac Output and Blood Pressure, *Proc. Soc. Exper. Biol. & Med.* **31**:36, 1933.

5. Johnson, G. S., and Blalock, Alfred: Experimental Shock: XII. A Study of the Effects of Hemorrhage, of Trauma to Muscles, of Trauma to the Intestines, of Burns and of Histamine on the Cardiac Output and on Blood Pressure of Dogs, *Arch. Surg.* **23**:855 (Nov.) 1931.

6. Underhill, Frank P., and Kapsinow, Robert: The Alleged Toxin of Burned Skin, *J. Lab. & Clin. Med.* **16**:823 (May) 1931.

7. Phemister, D. B.: The Vascular Properties of Traumatized and Laked Bloods and of Blood from Traumatized Limbs, *Ann. Surg.* **87**:806 (June) 1928.

experiment of the importance of local loss of fluid into the tissues in the production of secondary traumatic shock:

Furthermore, necropsy examination of the traumatized limb showed increase in limb volume from hemorrhage which was sufficient to account for the fall in blood pressure. In fact, the volume of blood that it was necessary to withdraw intermittently in the course of an hour in order to kill an animal was always less than the increase in volume of the traumatized limb of the other animal, which was due very largely to hemorrhage in the tissues.

Two years later Blalock<sup>8</sup> and Parsons and Phemister<sup>9</sup> worked out the extent of this loss. These authors repeated the old experiments of Bayliss and Cannon<sup>10</sup> but amputated the traumatized limb at a higher level. They compared the weight of the traumatized and of the opposite normal limb. Parsons and Phemister found this difference sometimes to be as much as 60 per cent of the total volume of blood. Later Blalock<sup>11</sup> used this bisection method to determine the local loss of fluid in cases of burns, and he found that as in cases of traumatic shock the local loss of fluid was sufficient to account for the death of the experimental animals.

Underhill, Kapsinow and Fisk<sup>12</sup> approached the problem of burns directly and came to practically the same conclusions as Blalock. From the work of these authors a brief résumé of the changes in secondary shock from a burn may be made as follows: Following a severe burn there is a gradual leakage of fluid from the blood stream into the burned tissues. This fluid has about the same concentration as blood plasma, its chloride content being a little higher than that of plasma and its sugar and nonprotein nitrogen contents about the same and its protein content being at least 80 per cent of that of plasma (Beard and Blalock;<sup>13</sup> Underhill.

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8. Blalock, Alfred: Experimental Shock: The Cause of the Low Blood Pressure Produced by Muscle Injury, *Arch. Surg.* **20**:959 (June) 1930.

9. Parsons, Eloise, and Phemister, D. B.: Haemorrhage and "Shock" in Traumatized Limbs, *Surg., Gynec. & Obst.* **51**:196 (Aug.) 1930.

10. Bayliss and Cannon, cited by Parsons and Phemister.<sup>9</sup>

11. Blalock, Alfred: Experimental Shock: VIII. The Importance of the Local Loss of Fluid in the Production of the Low Blood Pressure After Burns, *Arch. Surg.* **22**:610 (April) 1931.

12. Underhill, Frank P.; Kapsinow, Robert, and Fisk, Merl E.: Studies on the Mechanism of Water Exchange in the Animal Organism: I. The Nature and Effects of Superficial Burns, *Am. J. Physiol.* **95**:302 (Nov.) 1930; II. Changes in Capillary Permeability Induced by a Superficial Burn, *ibid.*, p. 315; III. The Extent of Edema Fluid Formation Induced by a Superficial Burn, *ibid.*, p. 325; IV. The Composition of Edema Fluid Resulting from a Superficial Burn, *ibid.*, p. 330; V. The Relationship of the Blood Chlorides to the Chlorides of Edema Fluid Produced by a Superficial Burn, *ibid.*, p. 334.

13. Beard, J. W., and Blalock, Alfred: Experimental Shock: VIII. The Composition of the Fluid that Escapes from the Blood Stream After Mild Trauma to an Extremity, After Trauma to the Intestines and After Burns, *Arch. Surg.* **22**:617 (April) 1931.

Kapsinow and Fisk<sup>12</sup>). The amount of this fluid was determined by cutting out the edematous tissues and weighing them after evaporation at constant temperature (Underhill, Kapsinow and Fisk<sup>12</sup>) and by bisection of the animal and comparison of the weight of the burned with that of the normal half (Blalock<sup>11</sup>). The former authors found that definite fluid had collected in six hours and continued to accumulate up to from twenty-four to thirty-six hours. In twenty dogs after an average of twenty-seven hours this fluid averaged 1.4 per cent of the body weight. The latter author found the average fluid after an average of fifteen hours equal to 3.34 per cent of the body weight in eighteen dogs. The difference in the amounts of fluid observed by these two authors is to be explained partly by the difference in method and partly by the difference in the severity of the burn. The burns in Underhill's animals were not severe enough to produce death, while nine of Blalock's eighteen dogs died following the burning. In animals such as the dog there is no blistering or weeping from the skin, but in human beings there is this additional factor affecting the loss of fluid. One of the actions of tannic acid as used in man by Davidson<sup>14</sup> and Wilson<sup>15</sup> is to stop this additional loss of fluid.

Because of this local loss of fluid there is a decrease in the volume of blood as shown by Roome, Keith and Phemister<sup>16</sup> for traumatic shock in general and by Blalock for burns in particular. This reduction in the volume of blood is accompanied by a reduction in cardiac output.<sup>5</sup> Vasoconstriction accompanies this reduction in cardiac output, and it is not until this falls as low as one third its normal value that the blood pressure falls appreciably. When this stage is reached the fall in blood pressure may be quite rapid. Along with these changes in the circulation are changes in the composition of the blood itself. In Underhill, Carrington, Kapsinow and Pack's<sup>17</sup> series of twenty-one patients who were burned in a theater fire at New Haven, the hemoglobin varied from 117 to 209 per cent. The extent of this rise in hemoglobin is of interest because in the experiments reported in the present paper I did not find such a marked rise at any time in animals dying of experimental burns. In Blalock's experiments the rise in hemoglobin was not so marked as in Underhill's patients, and in animals severely burned by

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14. Davidson, E. C.: Tannic Acid in the Treatment of Burns, *Surg., Gynec. & Obst.* **41**:202 (Aug.) 1925.

15. Wilson, W. C.: The Modern Treatment of Burns and Scalds, *Practitioner* **129**:183 (July) 1932.

16. Roome, N. W.; Keith, W. S., and Phemister, D. B.: Experimental Shock: The Effect of Bleeding After Reduction of the Blood Pressure by Various Methods, *Surg., Gynec. & Obst.* **56**:161 (Feb.) 1933.

17. Underhill, Frank P.; Carrington, George L.; Kapsinow, Robert, and Pack, George T.: Blood Concentration Changes in Extensive Superficial Burns, and Their Significance for Systemic Treatment, *Arch. Int. Med.* **32**:31 (July) 1923.

Underhill, Kapsinow and Fisk the rise in hemoglobin was also not so marked. These authors showed that the blood concentration often diminished just before death.

The point of view expressed in the preceding paragraphs has not been universally accepted as the entire explanation of the secondary shock stage of burns. This stage is often called that of toxic shock, the very name indicating a theory as to its causation. Bardeen,<sup>18</sup> in 1898, performed necropsies on five patients who died following severe burns. He found extensive changes in the lymphatic tissues, especially focal necroses of the germinal centers of the lymph glands and of the malpighian corpuscles of the spleen. He interpreted these changes as evidence of toxic action. Fender<sup>19</sup> studied the lymphatic tissues of burned rabbits, and although he found the same changes as Bardeen he came to less definite conclusions as to their origin, stating: "The theory of causation of death by a toxin cannot be said to rest upon adequate experimental work at present." Duodenal ulcer following burns has often been reported in the literature, the first descriptions being by Long<sup>20</sup> in 1840 and Curling<sup>21</sup> in 1842, and this has often been cited as evidence for the toxic theory. Underhill, Kapsinow and Fisk have shown, however, that in cases of burns produced experimentally on the trunk the intra-abdominal temperature may reach a very high point. It is quite possible that the changes found by Bardeen,<sup>18</sup> Fender,<sup>19</sup> Long<sup>20</sup> and others may merely be due to the physical effects of local hyperthermia. Blalock<sup>22</sup> has shown that generalized degenerative changes in some of the organs in dogs may result from hemorrhage alone. The same might be expected from the local accumulation of fluid in cases of burns without the interaction of any toxic agent. Only one necropsy has been performed at the University of Chicago Clinics in a case of fatal burn. This was performed on a 4 year old girl who died eleven days after a severe burn from hot water involving chiefly the anterior portion of the trunk. A typical Curling ulcer was found on the posterior wall of the duodenum 5 cm. below the pylorus. This ulcer might well have been on an infectious basis since three days before death there developed arterial and venous thrombi in the right arm and a large peritonsillar abscess from which *Streptococcus viridans* and *Staphylococcus aureus*

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18. Bardeen, C. R.: A Review of the Pathology of Superficial Burns, with a Contribution to Our Knowledge of the Pathological Changes in the Organs in Cases of Rapidly Fatal Burns, Johns Hopkins Hosp. Rep. 7:137, 1898.

19. Fender, Frederick A.: Lymphatic Pathology in Relation to the "Toxin" of Burns, Surg., Gynec. & Obst. 67:612 (Nov.) 1933.

20. Long, cited by Bardeen.<sup>18</sup>

21. Curling, cited by Bardeen.<sup>18</sup>

22. Blalock, A.: Traumatic Shock and Hemorrhage, South. M. J. 27:126 (Feb.) 1934.



were cultured. This case is also not inconsistent with Underhill, Kapsinow and Fisk's theory that the physical effects of the local heat are the important factor, since this patient's burns were chiefly over the anterior surface of the trunk.

The chief advocates of the toxic theory in recent years have been Robertson and Boyd,<sup>23</sup> who stated that "from a purely clinical point of view there seems to be no doubt that the burned tissues are responsible for the production of some toxin which is taken up by the blood stream." They went so far as to say that their toxin had a thermostable neurotoxic and a thermolabile necrotoxic element and contained primary and secondary proteoses. They found that blood or red cells from a burned animal when injected into normal animals produced all the symptoms of burn toxemia but that plasma alone produced no effects. From this they concluded that the toxin is present in or is adsorbed on the red cells. Alcoholic extracts of burned skin when injected into normal animals produced all the symptoms of burn toxemia, while skin from normal animals or from animals burned after death produced no such symptoms. Other authors have obtained results completely at variance with those of Robertson and Boyd. Underhill and Kapsinow's results indicate that the alcohol used in preparing Robertson and Boyd's extracts was the toxic agent and furthermore that normal skin was as toxic as burned skin. Underhill and Kapsinow found no difference following the injection of blood from burned animals and normal animals. They pointed out that Robertson and Boyd did not list their controls in detail, and finally stated: "Our experience with burns leads us to doubt the existence of a 'burn toxin,' and to believe that the persistence of this viewpoint is an obstruction in the way of clarification of the burn problem."

Other authors also obtained results which do not favor the toxic theory. Harkins, Wilson and Stewart,<sup>24</sup> working in Wilkie's laboratory, made extracts of normal and burned skin taken from rabbits at various intervals of from three minutes to forty-eight hours after burning. These extracts were prepared by the method of Chang and Gaddum<sup>25</sup> and were tested for acetylcholine equivalent as shown by the effect on the blood pressure of the cat and rabbit and on the rectus muscle of the frog. The active principle was found to be neither histamine nor acetylcholine, as the extracts were just as active in the rabbit given injections of atropine as in the rabbit or cat that did not receive the injections.

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23. Robertson, Bruce, and Boyd, Gladys L.: The Toxemia of Severe Superficial Burns, *J. Lab. & Clin. Med.* **9**:1 (Oct.) 1923.

24. Harkins H. N.; Wilson, W. C., and Stewart, C. P.: *Depressor Action of Extracts of Burned Skin*, *Proc. Soc. Exper. Biol. & Med.* **32**:913, 1935.

25. Chang, H. C., and Gaddum, J. H.: Choline Esters in Tissue Extracts, *J. Physiol.* **79**:255 (Oct. 6) 1933.

This indicates that the substance which was present in the approximate concentration of 1 microgram acetylcholine equivalent per gram of tissue was possibly similar to Euler and Gaddum's "P-substance."<sup>26</sup> Most important from the standpoint of the pathologic changes in cases of burns was the fact that the extract was equally potent when obtained from equal amounts of normal and of burned skin. Harris,<sup>27</sup> working in Lewis' laboratory and using earlier methods, found that up to thirty minutes the "histamine-equivalent" of burned and of unburned skin was the same, but one hour after burning the potency of burned skin was only 50 per cent that of normal skin. The later work of Harkins, Wilson and Stewart indicates that there is no detectable histamine in normal or in burned skin.

Harrison and Blalock<sup>28</sup> also found no evidence of burn toxin in their experiments. They found that transplantation of burned skin had no effect on the recipient, that débridement of the burned area markedly shortened the survival period of dogs and that transfusion of blood from burned to normal dogs was practically without effect. Underhill, Kapsinow and Fisk found that absorption of phenolsulphonphthalein and strychnine was very slight from burned areas. The work of Parsons and Phemister,<sup>9</sup> who tested the toxic properties of blood from traumatized limbs, has an indirect application to the problem of burns. These authors found that blood from a traumatized limb circulated through the femoral artery of another dog by Anrep's viviperfusion apparatus produced no vasodilation unless the blood itself was traumatized outside the body, and then it acted no differently from similarly treated normal blood. The effect of extracorporeal trauma was thought to be due to hemolysis. Parsons and Phemister also showed that in traumatic shock hemolysis could not be a factor because blood taken from the jugular vein of dogs suffering from the effects of severe trauma to the extremities showed no hemoglobin in the plasma.

At the present time, therefore, the two chief theories as to the causation of secondary shock in cases of burns are the toxic theory which postulates that the shock is due to a burn toxin and the physical theory which states that the shock is due to local loss of fluid from the blood into the burned tissues. The physical theory involves: (1) a local leakage of fluid into the burned tissues; (2) a resultant change in circulation including diminished volume of blood, diminished cardiac output and finally collapse of blood pressure, and (3) a resultant concentration of

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26. Euler, U. S., and Gaddum, J. H.: An Unidentified Depressor Substance in Certain Tissue Extracts, *J. Physiol.* **72**:74 (June 6) 1931.

27. Harris, Kenneth E.: Observations upon a Histamine-Like Substance in Skin Extracts, *Heart* **14**:161 (Dec.) 1927.

28. Harrison, W. G., Jr., and Blalock, Alfred: A Study of the Cause of Death Following Burns, *Ann. Surg.* **96**:36 (July) 1932.

the blood with increased percentage of hemoglobin. To test the time relation between certain of these changes by a continuous record the following experiments were devised.

#### METHOD

Animals under complete anesthesia were used in all experiments, and none that were burned were allowed to recover. Except for one rabbit, dogs were used in all experiments. They were weighed accurately and anesthetized with sodium barbital (0.3 Gm. per kilogram of body weight intraperitoneally), occasionally supplemented by a little ether. The blood pressure was determined by placing in the carotid artery a cannula which was connected to a mercury manometer. The percentage of hemoglobin was determined by the Sahli method, and hematocrit readings were made with the Van Allen hematocrit. The hair was removed from the body and extremities of the animals by the use of either fine clippers or a razor. The longitudinal midlines on both the dorsal and the ventral surface were marked with india ink. Female animals were catheterized so as to prevent urination during the experiment and consequent loss of fluid. If the animal had a long tail it was fastened to the midline of the abdomen so as to prevent movement during the experiment. The animal was then encased in a plaster cast covering all parts except the extremities and the tip of the snout. The openings in the cast were symmetrically enlarged so as to expose the chest and axilla on each side, and an opening was made over the front of the neck for insertion of the tracheal and carotid cannulas. The animal was then placed on the tipping apparatus devised by me.<sup>29</sup> An animal placed on this apparatus is in a state of balance, and any lateral shift in fluid will cause it to tip with a resultant change in the position of the marker on the kymographic drum. In earlier experiments<sup>29</sup> the openings in the cast were made only on the side to be burned. This had the disadvantage of causing a tipping of the apparatus at each breath, because the exposed side of the chest would puff out and cause an increase in weight. Furthermore, in certain control experiments as the animal relaxed when near death it would sag toward the exposed side. In all later experiments, therefore, the openings were made symmetrically.

Strips of wet plaster were placed along each side of the animal between the body cast and the balanced tray. This, when hardened, produced a solid union between the animal and the tray. An additional feature was the application of cuffs similar to those on operating tables to hold the front paws rigid but at the same time not stretched too tightly above the head. This was done for two reasons: First, when the paws were fastened too tightly with ropes they tended to become edematous, and it was thought that this edema if not symmetrical might cause tipping, and second, in certain early tracings the blood pressure showed the type of antemortem rise seen in cases of asphyxia such as might be produced by interfering with the accessory movements of respiration.

Control balance and blood pressure tracings were started, and blood was obtained by puncture of a hindpaw for an estimation of the percentage of hemoglobin and the hematocrit reading. The exposed limbs, inguinal region, chest and axilla on one side were then burned over a period of ten minutes by the direct application of a bunsen flame, chiefly from below through the holes in the tray. The resultant fluid shift to the burned side was recorded as a tracing. The tracing

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29. Harkins, Henry N.: Shift of Body Fluids in Severe Burns, *Proc. Soc. Exper. Biol. & Med.* **31**:994 (May) 1934.

was continued until death, the blood pressure being taken intermittently and the percentage of hemoglobin and the hematocrit readings being determined at approximately hourly intervals. The sensitivity of the balance was then determined by counterbalancing the fluid shift by weights. It was observed at autopsy that in the sized animals used most of the edematous tissue was about 8 cm. from the midline of the tray. Hence the counterbalance weights were placed at this distance from the midline of the tray and at the same distance above the tray as the regions that tended to be most edematous. This was called the counterbalance method of determining the fluid shift. It is obviously quite rough but is probably as accurate as the second method used. The entire animal was then removed from the cast and weighed to determine the total loss of weight. It was bisected up to the neck by the method of Blalock,<sup>11</sup> and the two lateral halves were weighed after the head, tail, viscera, diaphragm and spinal column were discarded. This was called the direct weight method of determining the fluid shift.

The chief inaccuracy of the counterbalance method is the choice of the distance from the midline to apply the weights. The extreme limits of error in one experiment were determined as follows: At 8 cm. the counterbalance method gave a

TABLE 1.—*Variation in a Series of Seven Control Dogs, Blalock's Bisection Method Being Used*

Experiment	Weight of Dog, Gm.	Weight of Right Side, Gm.	Weight of Left Side, Gm.	Difference, Gm.	Difference as per Cent of Body Weight
9.....	4,600	1,237	1,265	28	0.61
10.....	5,862	1,492	1,537	45	0.77
11.....	6,030	1,643	1,603	40	0.66
18.....	24,000	6,948	6,920	28	0.12
20.....	11,460	3,643	3,620	23	0.20
21.....	24,000	6,948	6,920	28	0.12
23.....	12,070	3,643	3,620	23	0.19

fluid shift of 130 Gm. The burned region extended from 3 cm. from the midline to 13 cm. from the midline of the tray. If 3 cm. was used, the counterbalance method gave a fluid shift of 380 Gm., and if 13 cm. was used it gave a fluid shift of 80 Gm. The error is considerably less than these limits, however. It is also obvious that since the balanced tray is suspended from above, the midline of the tray is not the same as the fulcrum of the balance. The sensitivity of the balance must be tested in each experiment since it varies with the weight of the animal according to the well known formula:

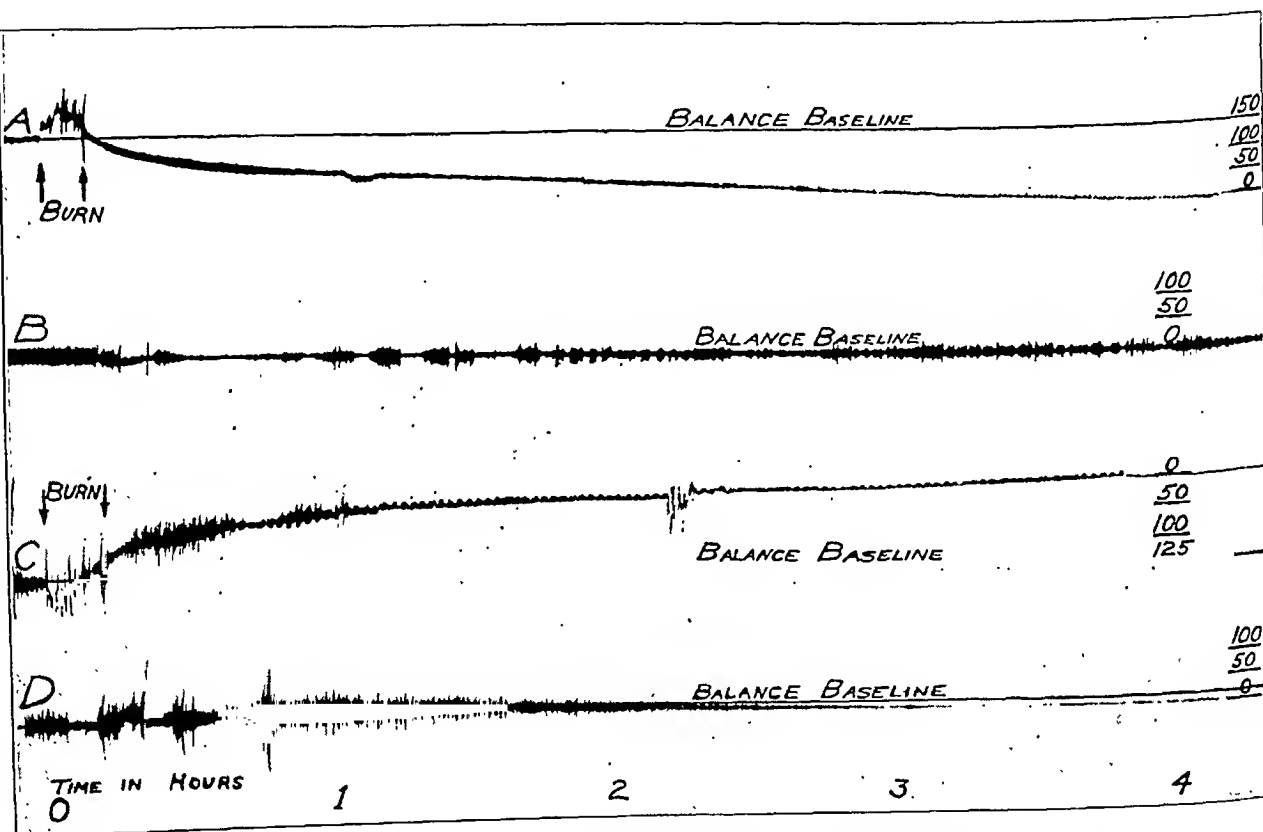
$$\text{Sensitivity} = \frac{\text{length of arm}}{\text{total weight system} \times \text{distance from center of gravity to fulcrum}}$$

The direct weight method is also not entirely accurate for small animals. Normal animals were bisectioned to test the accuracy of the method, the differences being shown in table 1.

## RESULTS

Eight burn experiments and sixteen control experiments of various types were performed. In the eight burn experiments the interval between the application of heat and the death of the animal varied from one hour and thirty minutes to six hours and thirty minutes. In certain experiments there was a slight decrease in the weight of the burned side during the burning process as shown by a tipping of the apparatus to the opposite side. However, in most instances the burned side was

already heavier before the burning was completed. The fluid shift was rather rapid for some time and then became less rapid in the form of a decelerating curve till the time of death. The tracings show the results obtained in two typical burn experiments and two typical control experiments. The degree of shift in other experiments is given in table 2, from which it is seen that at the end of an hour from 41 to 77 per cent of the ultimate shift had already occurred. This suggests that even one hour may be too long an interval in which to include primary neurogenic shock if the time definition of primary shock is used. On



Tracings obtained in two burn experiments and in two control experiments performed on the balanced apparatus: *A*, burn experiment 7; *B*, control experiment 11; *C*, burn experiment 6, and *D*, control experiment 9. In experiment 7 the burned side is away from the kymographic drum, so that the shift to the burned side causes the recording point to move downward. In experiment 6 the burned side is toward the drum, and the shift causes the recording point to move upward.

the other hand, it might be objected that the fluid shift in certain instances was smaller in proportion to the body weight of the animal than the results obtained by other authors; e. g., in eight experiments the shift at death averaged 2.2 per cent of the body weight, whereas in nine experiments of Blalock it averaged 3.2 per cent of the body weight at death. Thus the restraining effect of the cast on respiration may have caused the animals to die sooner than otherwise.

To determine the amount of weight lost during the process of burning alone, animals were weighed before and after burning. A live animal lost 12 Gm. during burning of the right side for ten minutes. After burning of the left side for five minutes it lost an additional 10 Gm. A dead dog lost 10 Gm. in five minutes and 17 Gm. in ten minutes of burning of the right side. In each case an equivalent area was burned. It thus seems that the actual burning alone causes little loss of weight. By weighing the animal just before and at the end

TABLE 2.—*Fluid Shift in Eight Burn Experiments Performed on the Balanced Apparatus\**

Experiment.....	1	2	3	4	5	6	7	8
Weight, Kg. ....	3.3	5.0	4.0	5.0	5.9	5.2	6.3	6.5
Fluid shift in:								
10 minutes.....	..	0	0	24	35	13	0	-21
20 minutes.....	..	25	17	..	54	33	19	14
30 minutes.....	..	32	25	56	62	50	31	32
45 minutes.....	..	46	33	60	69	57	38	39
1 hour.....	..	41	42	64	77	67	46	46
1 hour 30 minutes.....	..	51	67	70	100	73	58	57
2 hours.....	..	57	75	72	..	77	65	61
2 hours 30 minutes.....	..	65	91	79	..	90	77	75
3 hours.....	..	70	100	84	..	93	81	86
3 hours 30 minutes.....	..	76	..	86	..	100	92	93
4 hours.....	83	81	..	88	..	..	100	96
4 hours 30 minutes.....	..	84	..	92	..	..	..	100
5 hours.....	..	87	..	96	..	..	..	..
5 hours 30 minutes.....	100	94	..	100	..	..	..	..
6 hours.....	..	97	..	..	..	..	..	..
6 hours 30 minutes.....	..	100	..	..	..	..	..	..
Time of death.....	5 hr. 30 min.	6 hr. 30 min.	3 hr.	5 hr. 30 min.	1 hr. 30 min.	3 hr. 30 min.	4 hr. 30 min.	5 hr. 15 min.
Shift by counterbalance.....	24	170	45	140	145	125	155	125
Shift as per cent of body weight.....	0.7	3.4	1.1	2.8	2.5	2.4	2.5	1.9
Weight of burned side.....	..	..	1,100	1,381	1,630	1,367	1,822	1,890
Weight of normal side.....	..	..	1,011	1,251	1,543	1,206	1,687	1,755
Weight difference.....	..	..	89	130	87	161	135	135
Weight as per cent of body weight.....	..	..	2.2	2.6	1.5	3.1	2.1	2.1

\* The fluid shift is calculated from the tracing and expressed as per cent of the final displacement. The negative shift at the end of ten minutes in experiment 8 denotes the temporary decrease in weight of the burned side.

of a complete experiment the total loss from burning, the fluid lost from the lungs and what little is lost from the skin of a dog were measured. An animal weighing 6.5 Kg. lost 55 Gm. in four hours; one weighing 7 Kg. lost 116 Gm. in four hours, and one weighing 6.5 Kg. lost 94 Gm. in ten hours. This represents an average loss in weight from all causes including burning of 2.5 Gm. per kilogram per hour. Roome and Wilson<sup>30</sup> observed five control dogs over an average period of forty-six hours and twelve minutes and anesthetized them with an average of 276 mg. of sodium barbital per kilogram of body weight. The loss of weight at the end of this period averaged 9.11 per cent of the body weight. This corresponds to 1.9 Gm. per kilogram per hour,

30. Roome, Norman W., and Wilson, Harwell: To be published.

which is only a little less than that lost per hour by the burned animals used in the experiments described in the present paper. Furthermore, Roome and Wilson's figures can be interpolated for a shorter period since they observed the loss of weight at different intervals of time and found that it was directly proportional to the elapsed time.

The blood pressure usually remained near the normal level until the animal was near death, at which time the pressure collapsed rather suddenly. The hemoglobin percentage and the hematocrit reading rose following the burn but fell slightly before death. This may be due to

TABLE 3.—*Comparison of Fluid Shift, Blood Pressure, Hemoglobin Percentage and Hematocrit Reading in Experiment 8\**

Time	Shift, per Cent	Blood Pressure	Hemoglobin, Percentage	Hematocrit Reading
Control	0	132	93	45
10 minutes	-21	140	..	..
20 minutes	14	144	..	..
30 minutes	32	142	..	..
45 minutes	39	...	..	..
1 hour	46	...	..	..
1 hour 30 minutes	55	124	109	59
2 hours	61	...	...	..
2 hours 30 minutes	75	130	138	58
3 hours	86	...	...	..
3 hours 30 minutes	93	112	130	60
4 hours	96	34	122	62
4 hours 15 minutes	100	0	113	56†

Anesthetic = 1.9 Gm. of sodium barbital

Animal weight = 6,500 Gm.

Animal weight at end = 6,445 Gm.

Loss of weight = 55 Gm., or 0.8 per cent of body weight

Weight of burned side = 1,890 Gm.

Weight of normal side = 1,755 Gm.

Weight difference = 135 Gm., or 2.1 per cent of body weight

Counterbalance difference = 125 Gm., or 1.9 per cent of body weight

\* It is seen that the fluid shift is followed by an increase in blood concentration while the blood pressure remains almost normal until near death, when it suddenly collapses. The fluid shift is calculated from the tracing and expressed as per cent of the final displacement. The negative shift at the end of ten minutes denotes the temporary decrease in weight of the burned side.

† Last sample from heart's blood, immediately after death.

the lowered blood pressure diminishing the hydrostatic pressure within the blood vessels and allowing water to return from tissues. From this it seems that the fluid shift and changes in the concentration of the blood follow each other rather closely, while the blood pressure remains near normal, only to collapse at the end. This may indicate that in clinical cases the patient may be in a serious condition even though the blood pressure is near normal and that the shock is secondary shock. The changes are compared for a representative experiment in table 3.

Three successful control experiments were made identical with the burn experiments. They showed no fluid shift at the end of ten, twelve and seventeen hours. After this time the effect of the barbital wore off, and the resultant struggling caused a slight movement. The absence

TABLE 4.—Changes in Blood Pressure, Hemoglobin Percentage and Hematocrit Reading in Six Control Dogs

Experiment 10*				Experiment 11*				Experiment 21				Experiment 22				Experiment 23				Experiment 24			
Time of Obser-	Blood Pressure	Hemoglobin Percentage	Hematocrit Reading	Time of Obser-	Blood Pressure	Hemoglobin Percentage	Hematocrit Reading	Time of Obser-	Blood Pressure	Hemoglobin Percentage	Hematocrit Reading	Time of Obser-	Blood Pressure	Hemoglobin Percentage	Hematocrit Reading	Time of Obser-	Blood Pressure	Hemoglobin Percentage	Hematocrit Reading	Time of Obser-	Blood Pressure	Hemoglobin Percentage	Hematocrit Reading
Onset	120	80	29	Onset	122	106	54	Onset	154	86	40	Onset	131	109	54	Onset	136	112	48	Onset	118	85	43
5	122	89	31	10	132	112	50	10	142	88	42	10	133	113	52	9	130	113	49	9	124	84	41
15	118	88	37	14	140	105	51	15	123	78	40	14	132	106	49	14	120	112	47	19	116	91	42
19	111	75	41	..	..	..	..	24	123	67	33	18	133	103	49	16	102	91	41	..	..	..	..
Weight of dog = 5.892 Kg.				Weight of dog = 6 Kg.				Weight of dog = 21 Kg.				Weight of dog				Weight of dog				Weight of dog = 19.5 Kg.			
Before = 5.892 Kg.				..				..				Before = 12.975 Kg.				Before = 12.070 Kg.				..			
After = 5.553 Kg.				..				..				After = 12.711 Kg.				After = 11.922 Kg.				..			
Loss = 301 Gm.				..				..				Loss = 264 Gm.				Loss = 148 Gm.				..			
Weight of				Weight of				Weight of				Weight of				Weight of				..			
Right side = 1.537 Kg.				Right side = 1.643 Kg.				Right side = 6.948 Kg.				Right side = 6.920 Kg.				Right side = 3.643 Kg.				..			
Left side = 1.492 Kg.				Left side = 1.603 Kg.				Left side = 6.920 Kg.				Left side = 6.920 Kg.				Left side = 3.620 Kg.				..			
Difference = 45 Gm.				Difference = 45 Gm.				Difference = 28 Gm.				Difference = 28 Gm.				Difference = 23 Gm.				..			

\* Additional balance readings performed in experiments 10 and 11 showed no shift.



of shift in two of these controls is shown in the tracing. A control was made by burning plaster of paris of about the same age as that used on the experimental animals on the balance and by burning a dead dog in a plaster cast. The plaster alone showed a shift equivalent to a loss of weight of 14 Gm. during the burning but no further shift at the end of an hour. The dead dog lost 60 Gm. during the burning (counter-balance) or 63 Gm. (direct weight), and shifted back toward normal an estimated amount of 20 Gm. in seventy-five minutes. All of these changes are less than the shift produced by burning live animals.

Six control experiments were made to determine the changes in blood pressure, hemoglobin percentage and hematocrit reading in unburned animals placed on the apparatus. They show (table 4) that the changes in blood pressure, percentage of hemoglobin and hematocrit reading are all less than those produced by burns.

#### COMMENT

The results of these experiments are in general agreement with those of workers who advanced the hypothesis that local loss of fluid from the blood vessels into the burned tissues is a factor in the production of shock and that the type is secondary. A graphic method of recording the accumulation of this fluid shows that the method of producing burns used in the experiments caused the accumulation to be quite rapid. In several experiments more than half of the ultimate amount of fluid had collected in an hour. The total amount of fluid shift was not as great as that reported by some other observers but this may be because of its rapid formation. The concentration of the blood as shown by increase in the percentage of hemoglobin and in the hematocrit reading was roughly proportionate to the loss of fluid, but the blood pressure remained near normal until death approached, and then it fell rapidly.

The time relations of the various local, circulatory and hematologic changes in cases of shock are of importance in the differentiation of its various types. Experimental shock may be classified as primary and secondary, the decrease in blood pressure being said to precede reduction in cardiac output in the former and to follow it in the latter. Little evidence for primary shock was found in the experiments reported in the present paper. The accumulation of fluid in the burned tissues begins in many cases before the burning is completed, and the rapidity of this accumulation may account for many of the cases that have been mislabeled primary neurogenic shock. Psychogenic factors have been excluded from these experiments, and neurogenic influences could not be demonstrated although they could not be excluded. The accumulation of fluid in the tissues has been shown to be of importance, and this places the reaction in the category of secondary shock.

## SUMMARY

A graphic method of recording the local accumulation of fluid in cases of burns is presented. This accumulation begins at the time of the burn and continues in the form of a decelerating curve until death. Accompanying the collection of fluid is a simultaneous increase in the concentration of blood as shown by an increase in the percentage of hemoglobin and in the hematocrit readings. After most of the fluid has accumulated, the fall in blood pressure sets in and continues rapidly until death occurs in a state of secondary shock.

# A STUDY OF DISRUPTIONS OF ABDOMINAL WOUNDS

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Within the past year, the subject of disruption of abdominal wounds has enjoyed a belated prominence in the writings and at the meetings of surgeons. Sporadic papers had been published in the leading journals, but on Nov. 8, 1933, an entire evening's symposium by five leading surgeons of New York<sup>1</sup> was presented by the New York Surgical Society. Therein it was revealed that the incidence of this postoperative disaster was as high as 2 per cent, with a mortality rate ranging from 28 to 53 per cent.

Several of the participants in the aforementioned symposium contended that the incidence was undoubtedly higher because of the failure to recognize or record many of the cases. Similarly, Dr. Allen O. Whipple, who took part in the discussion, pointed out the inadequacy of statistics obtained from the record room as compared to those based on an accurate study of a series of laparotomies. With this in mind I have made a careful study of 1,560 laparotomies performed in all the services at the New York Post-Graduate Hospital over a period of a year and a half, from January 1933 to July 1934. Inguinal and femoral herniotomies, which might technically be considered laparotomies, were excluded from this series.

The particular condition of disruption of abdominal wounds has been known by many names, but regardless of the descriptive term used, the result is the same—a postoperative dissolution in the continuity of all the layers of tissue involved in the operative repair of the wound in the anterior abdominal wall, in part or in its entirety. In this respect, too, the statistics relating to incidence err, for it has been noted that in the contributions of some writers only the wounds that gape or from which viscera protrude are so classified. Thus, if this report were to deal only with gaping disrupted wounds my series of 20 cases would be reduced to 13, and if only the cases of evisceration were presented the number would shrink to 3. In presenting this study I have included all cases in which a partial or an entire separation of the abdominal

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From the Surgical Service, New York Post-Graduate Medical School and Hospital, Columbia University.

1. Meleney, F. L., and Howes, E. L.: Disruption of Abdominal Wounds with Protrusion of Viscera, *Ann. Surg.* 99:5 (Jan.) 1934; Colp, R.: Disruption of Abdominal Wounds, *ibid.*, p. 14; Grace, R. V.: Disruption of Abdominal Wounds, *ibid.*, p. 28; White, W. C.: Disruption of Abdominal Wounds, *ibid.*, p. 34; Heyd, C. G.: Disruption of Abdominal Wounds, *ibid.*, p. 39.

wound from the skin through the peritoneum occurred. It was thought that only in this way could a fair analysis be made, despite the apparent increase in frequency.

A further fallacy of statistics per se is demonstrable. Based on a study of 1,560 consecutive laparotomies, the incidence of disruption is 1.28 per cent. It so happened that 6 dehiscences occurred in the last sixteen days of the eighteen month period. If the study excluded these disruptions the incidence for 1,500 cases would be 0.93 per cent. Again, if one were to consider only the cases of actual evisceration, of which there were but 3, the frequency would be 0.19 per cent.

Historically, the condition of rupture of a wound has unquestionably been an ominous occurrence since the inception of abdominal surgery. Over a quarter of a century ago reports are found by Ries<sup>2</sup> and Madelung<sup>3</sup> on the subject. The first author reported his experiences with a small group of cases in this country, while the second presented a series of 157 cases in Germany. Since that time intermittent reports have emanated from various centers on the globe, culminating in the monumental work of Sokolov<sup>4</sup> of Leningrad, U. S. S. R., who reported over 700 cases collected from the records of European surgeons to whom he directed his questionnaire. A truer idea of the prevalence of the complication may be gained from the knowledge that this number represents the response of only 233 of 1,140 surgeons to whom Sokolov sent his queries.

#### RÔLE OF VARIOUS ETIOLOGIC FACTORS

My prime incentive in undertaking this study was principally directed toward the etiologic factors involved, with the purpose of preventing as many complications of this kind as possible. Before entering into such a discussion, however, my group of cases will be analyzed. The appended table contains the salient features of this analysis.

*Age.*—The condition usually occurs in persons in the fourth, fifth and sixth decades of life. If the number of appendectomies is excluded from the total number of laparotomies performed, one finds that the ages of most of the operative subjects in this series fell in the period of the three decades just mentioned. Disruptions have been reported to occur in infants, especially in those with hypertrophic pyloric stenosis.

*Sex.*—This factor seems to play a rôle in that the incidence among males exceeds that among females. The ratio in this series was slightly

2. Rics, E.: On Post-Operative Separation of Laparotomy Wounds, *Am. J. Obst. & Gynec.* 60:569 (Oct.) 1909.

3. Madelung, O.: *Arch. f. klin. Chir.* 75:347, 1905.

4. Sokolov, S.: Post-Operative Rupture of Abdominal Wounds with Protrusion of Viscera, *Vestnik khir.* 65-66:219, 1931; abstr., *Internat. Abstr. Surg.* (*Surg., Gynec. & Obst.*) 55:157 (Aug.) 1932.

below 6:1. Sokolov reported a ratio of 2:1, whereas reversed values have been reported from centers in which most of the operations are performed for gynecological conditions. An important factor to consider is the apparent ability of most women to tolerate operations better than men who have worked hard, owing to economic strife, and who may show the effect of prolonged use, and abuse, of alcohol or nicotine. A factor may be the abdominal type of breathing in men, as compared to

*Analysis of Twenty Cases of Disruption of Abdominal Wounds*

Age, Years	No. of Cases	Drainage	No. of Cases
20-29.....	1	Employed.....	9
30-39.....	1	Not employed.....	11
40-49.....	5		
50-59.....	8	Tension Sutures	
60-69.....	5	Employed.....	15
Sex		Not employed.....	5
Men.....	17		
Women.....	3	Condition of Postoperative Wound	
Primary Illness		Clean.....	13
Carcinoma.....	8	Exposed to digestive ferments.....	3
Disease of the biliary tract.....	6	Infected.....	4
Chronic pelvic peritonitis.....	2		
Peptic ulcer.....	3	Date of Disruption, Postoperative Day	
Cirrhosis of liver.....	1	4th.....	1
Preoperative Condition		5th.....	3
Emaciation.....	12	6th.....	3
Obesity.....	3	7th.....	3
Jaundice.....	2	8th.....	3
Arteriosclerosis.....	3	9th.....	2
Postoperative Course		10th.....	0
Undue restlessness.....	15	11th.....	4
Distention.....	15	12th.....	1
Vomiting.....	14	Treatment	
Gastric lavage.....	12	Packing and strapping.....	6
Autolavage.....	2	Secondary suture.....	14
Hiccup.....	9		
Pulmonary complications.....	16	Outcome	
Type of Incision		Living.....	9
Superior right rectus.....	13	Dead.....	11
Inferior left rectus.....	3		
Paramedian hypogastric.....	3		
Right rectus para-umbilical.....	1		

the thoracic type of respiration in most women, who also have a greater elasticity of the abdominal wall.

*Primary Illness.*—Colp<sup>1</sup> has referred to the primary disease as the most important factor underlying the disruption of a wound. I shall discuss this assertion later in the paper in dealing with the etiologic factors. In 2 of the 8 cases of carcinoma the tumor was localized in the sigmoid flexure, in 2 cases in the stomach and in 1 in the ascending colon, pancreas, fallopian tube and testis, respectively. There were 128 cases of malignant growth among the 1,560 laparotomies, making the incidence of disruption 6.25 per cent, as compared to the frequency of 1.28 per cent for all cases. In all the 6 cases of disease of the biliary tract, cholecystitis, cholelithiasis and varying degrees of pancreatitis

were shown. In 2 cases choledochostomy was performed with insertion of indwelling T-tubes in the common duct. The 6 remaining cases included 2 of gastric and 1 of duodenal ulcer, 2 of chronic pelvic peritonitis with associated adnexal disease and 1 of cirrhosis of the liver in which an exploratory operation was performed.

*Preoperative Condition.*—The condition of the patient before operation is a substantial factor in predisposition to disruption of a wound. In 12 cases of the present series marked emaciation was shown, 1 patient, a man, having lost 40 pounds (18.1 Kg.) in one and a half months. Conversely, 3 patients showed marked obesity. Both emaciation and obesity, as will be shown later, have a physiologic relationship to dehiscence. Jaundice was present in 2 cases, and generalized arteriosclerosis in 3.

*Postoperative Course.*—Practically all the patients whose wounds subsequently disrupted had a stormy postoperative course, as indicated in the table. Restlessness, more marked than is normally seen postoperatively, was present in three fourths of the cases. Distention was marked in a similar number. The frequency of vomiting with subsequent gastric lavages was also high, while hiccup proved troublesome in 9 instances. Pulmonary complications occurred in 16 of the 20 cases cited. In 5 of these cases, the patients had definite bronchopneumonia. In all, 46 of the 1,560 subjects had pulmonary complications. This number represents a general incidence of 2.9 per cent, as compared to the prevalence of these complications in 80 per cent of the group with disruptions. Other observers have recorded the same high frequency for such postoperative complications as coughing, hiccup, nausea and vomiting and distention.

*Operative Technic.*—The elements inherent in the patient favoring disruption having been presented, the question of operative technic may be considered. Incisions in the epigastric region, especially the approach to the gallbladder and stomach through a high right or left rectus incision, show, both in this series and in the cases reported by other investigators, the greatest frequency of dehiscence. In order to better evaluate the relationship of the location of the incision to disruption, I have analyzed the total number of abdominal incisions. Five hundred and forty-five incisions were located in the right lower quadrant, all of which were low right rectus wounds with the exception of 2 McBurney incisions. None of the 545 wounds disrupted. Of 390 incisions in the right upper quadrant and the epigastrium 13 disrupted, an incidence of 3.3 per cent. Three of 501 incisions in the hypogastric region disrupted—an incidence of 0.6 per cent. Dehiscence occurred in only 1 of 69 para-umbilical incisions, and this was a reentry through a freshly healed wound. Three of a total of 49 low left rectus wounds disrupted. This

relatively high frequency is easily explained in that 2 were colostomy wounds and 1 was a fecal fistula, all of which became grossly infected. No dehiscence occurred among the 6 subcostal incisions. A false impression of the frequency of disruption with regard to localization results from isolated reports. For example, Madelung reported a series of 124 disrupted wounds below the umbilicus and only 16 above it. However, most of his operative cases were gynecological—hence the discrepancy in the statement that the majority of disruptions occur in the upper part of the abdomen.

Except for minor individual variations, the usual closure of a laparotomy wound employed at the New York Post-Graduate Hospital is effected for the peritoneum with no. 1 or 2 plain catgut in a continuous suture. The muscle is reunited by some surgeons with the same material. Fascia is apposed with no. 1 or 2 chromic gut in a continuous suture, and the skin is closed with black silk. Tension sutures of dermal suture material, silkworm gut or braided silk, either of the circular or of the lateral button type, are used at the discretion of the operator. In cachectic persons Erdmann,<sup>5</sup> who attributes many disruptions to the too rapid absorption of catgut due to what he terms "tissue hunger," often uses chromic catgut throughout or heavy braided silk in through-and-through sutures. In the average case sutures of the skin are removed between the eighth and the tenth day, and the tension sutures between the tenth and twelfth day. Binders are not applied as a routine. Some surgeons insist on their use, while others order them only in selected cases. There is no question of the support and counterpressure afforded by the binder to the patient who is coughing or vomiting. However, some surgeons believe that the attendant fixation of the upper abdominal muscles and the limitation of costal excursions in the bedridden patient predispose to pulmonary atelectasis.

In two thirds of the cases of disruption tension sutures of the dermal suture material, silkworm or braided silk were used. All of these sutures included fascia and were of the circular type, except in 2 cases in which lateral buttons were used. It is interesting to note that in 1 of these cases the intra-abdominal disruptive forces (coughing and vomiting) were such as to cause a spontaneous rupture of two of the silkworm tension sutures. Binders had been used in two thirds of the cases prior to, and were employed in all following, the repair of the disrupted wound. Drainage in the form of cigaret tampons, rubber tissue or iodoform gauze was used in 9 cases, while 11 wounds were closed without drainage.

Postoperatively, 13 of the wounds were clinically clean. Three were exposed to drainage from the biliary tract, while 4 were grossly infected after intestinal surgical procedure. In treating the patients with the

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5. Erdmann, J. F.: Personal communication.

latter type of incisions, the wounds were purposely separated superficially, but complete dissolution followed the infection. Suppuration in wounds was shown by Howes and Harvey<sup>6</sup> to cause rapid absorption of even chromicized catgut. The day of the disruption of the wound, not always accurately determined, is indicated in the table. It is likely that the real dehiscence of the peritoneum and fascia occurred earlier than is indicated. Undoubtedly, the seepage of digestive ferments from the gastro-intestinal tract is a factor in the delay of healing of the wound. In the present series almost as many wounds with drainage disrupted as those which were closed tightly. It should be remembered, too, that roughly only 1 wound in every 10 of the total number was drained.

The disruptions of wounds reported in this paper occurred in the practice of eleven surgeons in different services at the New York Post-Graduate Medical School and Hospital. Eight house surgeons acted as first assistants at the operations. The point has been made that the tendency to pull on suture ligatures, the rough handling of tissues, the strangulation of tissue by ligatures tied too tightly or, conversely, the slipping of ligatures from faulty knots are all contributory to disruption of the wound. The wide distribution of cases just shown tends to prove that such defects in technic were accidental rather than due to a repeated error in performance by one person.

Few of the commentators on disruption of wounds have placed much stress on the importance of anesthesia. Colp stated: "It is quite evident that this plays an insignificant and unimportant part." Anesthesia in all the cases of disruption in this series was effected by gas and oxygen followed by ether. In 2 cases it was started with a spinal anesthetic, but persistent abdominal straining due to incomplete anesthesia necessitated recourse to ether. Since this study was completed 1 more dehiscence occurred, the patient having been under spinal anesthesia. Some workers may aver that the preponderance of disruptions in cases of inhalation anesthesia is merely a coincidence in a small series. Yet the sole anesthetic used in 154 of the 1,560 abdominal sections was spinal, and in this group, representing 10 per cent of the cases, no disruption occurred. Dr. Thomas H. Russell, of the staff of the New York Post-Graduate Medical School and Hospital has used spinal anesthesia for laparotomies whenever possible. He informed me recently that he has had, roughly speaking, 1 disruption in every thousand cases in the last five years. Of particular interest is the fact that Dr. Russell uses plain catgut for the peritoneum and fascia and never chromicized gut, which he believes to

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6. Howes, E. L., and Harvey, S. C.: Strength of Healing Wounds in Relation to Holding Strength of Catgut Suture. *New England J. Med.* 200:1285 (June 20) 1929.



be irritating to the tissues. From my studies I must conclude that inhalation anesthesia, with the ever present possibility of bronchial irritation or of major pulmonary complication together with distention, which is usually singularly absent with spinal anesthesia, plays a significant part in producing a stormy postoperative course and subsequent disruption of the wound.

*Diagnosis.*—While obvious in most cases, the diagnosis is often rendered difficult because of the insidiousness of the condition, especially when the appearance of the cutaneous incision belies the condition in the depth of the wound. Characteristically, profuse serosanguineous discharge appeared in 16 of the 20 cases in this series. It should be remembered that in the 4 remaining cases there was gross infection with purulent drainage. As has been noted, all the patients had rather eventful postoperative courses. That the nausea, vomiting and distention might have been the effect, rather than the cause, of the disruption is probable in a few cases. I have been impressed with the unusual amount of pain which several of the patients complained of prior to, and the marked well-being after, the disruption. There was no appreciable rise in the temperature or pulse rate, and the abdominal discomfort often disappeared after the accident. One patient frankly stated that he "felt something snap" in the area of the wound preceding the saturation of the dressing with serosanguineous fluid. In 4 of the cases dehiscence occurred within a few hours of the usual removal of the cutaneous sutures. A nurse's note on each chart recorded an antecedent spell of coughing in 3 cases and straining at stool in the fourth. In 2 other cases the sutures of the skin were removed to confirm the diagnosis. Lahey<sup>7</sup> recommended the exploration of the wound with a probe under strict asepsis in suspicious cases in which primary union of the skin exists. The various types of disrupted wounds and their appearance have been well described by Heyd.<sup>1</sup> I shall therefore pass over this aspect to a consideration of the methods of treatment.

*Treatment.*—The methods of treatment of disrupted wounds fall into two broad groups—that of packing and strapping and that of secondary suturing. The former method has been chosen most frequently as the conservative one in cases in which the condition of the patient was such as to forbid further intervention. Packing and strapping should, of course, be the initial procedure after the discovery of dehiscence, regardless of whether or not the patient will later be transferred to the operating room for resuture of the wound. In this group packing, usually with iodoform gauze, and strapping with broad adhesive tape were used for 6 patients, 4 being critically ill and 2 having only partially disrupted wounds.

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7. Lahey, F. H.: The Management of Some Complications Following Abdominal Operations, J. A. M. A. 89:1735 (Nov. 19) 1927.

Fourteen of the disrupted wounds were resutured, the particular technic varying with the operator. For the most part, through-and-through tension sutures of dermal material, silkworm gut or braided silk, taking in all the layers, were used. In 2 cases silver wire was used, the repair in 1 case being a modification of the method described by Shipley<sup>8</sup> of using the wires as tension sutures, with gradual shortening laterally until the edges of the wound are coapted. The anesthetic used in 7 cases was 2 per cent procaine hydrochloride locally, while a spinal anesthetic was administered in 5 cases and gas and oxygen in 2, in which, of course, no indication of evisceration was shown. Reduction in all cases was satisfactory, and in none of the cases of resuture did subsequent breakdown occur. Pool<sup>9</sup> advised the restoration of prolapsed intestines to the abdomen as quickly as possible. To minimize shock and mechanical difficulties in replacing distended intestinal loops, he suggested the insertion of a needle of small caliber through the wall of the intestine and the application of suction. There has been no occasion to use this method.

A study of the mortality figures reveals the fact that disruption of a wound is often a complication of what would have been a fatal outcome in any event. Eleven of the 20 patients died, a mortality rate of 55 per cent. Peritonitis occurred in 4 cases, but this developed prior to the disruption, although it must be admitted that the further complication only hastened the fatal outcome. Pneumonia, cardiorenal disease and carcinomatosis each claimed 2 victims, while cirrhosis of the liver was the cause of death of 1 patient. The mortality rate in the cases of resuture was 50 per cent, while in those in which the treatment was packing and strapping a mortality rate of 66 per cent was shown. In 4 of the latter group, however, the procedure was palliative because of the inevitable outcome. Other surgeons<sup>1</sup> have reported mortality rates ranging from 28 (Colp) and 33 per cent (Sokolov) to 53 per cent (White).

#### REPORT OF "EPIDEMIC" OF DISRUPTIONS

Of particular interest in this study was the occurrence of an "epidemic" of disruptions of wounds in the surgical service of the hospital during a period of two weeks in June 1934. The cases included 3 in the wards and 3 private cases, and the patients were in the hands of 6 operators. The accumulated data on these cases have already been presented, but because of the importance and gravity of the situation they merit closer scrutiny and consideration. Such a grouping, seemed more than mere coincidence.

8. Shipley, A. M.: Broken-Down Abdominal Incisions: A Method of Closure, *Ann. Surg.* **82**:452 (Sept.) 1925.

9. Pool, E. H.: Post-Operative Treatment, *New England J. Med.* **201**:510 (Sept. 12) 1929.

All the patients were men; 5 had epigastric incisions and 1 a right pararectus incision which, incidentally, was a reopening of a freshly healed wound for the secondary resection of a carcinoma of the ascending colon, an ileocolostomy having previously been performed. With the exception of the last case, in which the wound became infected and broke down, coughing of a persistent and racking nature occurred. More than average postoperative restlessness, with nausea, vomiting and marked distention (in 3 cases), was present. The anesthetics used in all cases were gas and oxygen followed by ether. In 1 case a spinal anesthetic was given, which failed. In 2 cases the characteristic profuse serosanguineous drainage preceded the removal of the sutures on the sixth postoperative day, while in 2 cases a similar drainage followed the removal of the silk from the skin on the seventh and eleventh day, respectively. In 2 cases in which a fatal outcome was inevitable, the disruptions were treated by packing and strapping. The 4 remaining patients were removed to the operating room within an hour or two of the accident, and resuture was performed. All 4 patients of this group recovered and left the hospital with apparently well healed wounds.

In analyzing the cases in the aforementioned group for a causative factor, particular suspicion fell on the material used for sutures. Tension sutures were utilized in 4 of the 6 cases. In all 6 a particular standard brand of no. 1 plain catgut (for peritoneum) and of no. 1 chromic catgut (for fascia) was used. Two other brands of catgut were also used in the operating rooms by operators with individual preferences, but in these 6 cases it was known that a newly arrived assignment of the catgut in question was employed. It is also true that other laparotomy wounds had been sutured with the same material during the same two week period, but the postoperative course in these cases was relatively uneventful.

Unfortunately, before definite evidence seemed to point to the catgut, the remainder of the stock was removed from the shelf and returned. Hence investigations of the tensile strength or quality of the catgut could not be carried out. It is my belief that in this particular group of disruptions the catgut was defective and failed in its normal duty of holding the tissues during the period of active healing of the wound in the face of the disruptive forces of cough, nausea, vomiting, distention and hiccup. In several of the wounds strands of catgut varying from  $\frac{1}{2}$  to 3 inches (1.27 to 7.62 cm.) in length were found with frayed ends, as if torn, the rest of the strand being intact except for slight swelling. It is probable that this particular batch of catgut, although it passed the minimum factory requirements, was poor in quality and deficient in tensile strength, because the same brand had been used previously without mishap.

## ANALYSIS OF TYPICAL LAPAROTOMY

In undertaking a study of the underlying etiologic factors one may diverge for a moment and consider a typical laparotomy. A simple incised wound is made through the abdominal wall, cleanly dividing the anatomic layers of skin, fascia, muscle and peritoneum. In this process a certain portion of tissue is unavoidably destroyed, together with blood vessels and nerve filaments. Ligatures are applied to bleeding points, and sutures are used in the closure of the wound. The technic varies with the operator, but the fundamental steps are unchanged. Howes, Sooy and Harvey<sup>10</sup> described the phenomena of exudation of blood or plasma and subsequent formation of fibrin along the latticework of which fibroblastic proliferation occurred after closure of the wound. The whole response is one of restoration of continuity. Damaged cells are restored or replaced, and new capillary buds appear. As a result of this fibroplasia an attendant increase in the strength and contraction of the wound occurs.

Howes<sup>11</sup> showed that during the first four or five days, the so-called latent period in healing just described, the strength of the wound is dependent on the holding power of the sutures and on the nature of the tissues. The thread strength of the suture, he demonstrated, was relatively unimportant and independent of the size of the suture. Whipple<sup>12</sup> cited the tensile strength of laparotomy wounds in cats in which the wounds sutured with catgut broke through the site of the incision even on the eighth day and thereafter the break took place through the surrounding tissues. With repair by silk, the suture line tore as late as the sixth day, the surrounding tissues tearing from the seventh day on. After the latent period in the healing of a wound the regenerative phase occurs, with fibroblastic proliferation which reaches a peak from the twelfth to the fourteenth postoperative day. It is this later phase which adds strength to the wound, taking the burden of cohesion of the tissues from the suture material.

Because the present study deals entirely with wounds repaired with catgut, silk being used only for closure of the skin, I shall confine myself to a consideration of the absorbable suture. Microscopic studies of plain catgut in vivo by Howes and Harvey<sup>13</sup> demonstrated the cellular reaction about the embedded suture. After the first day the strand of catgut becomes swollen and its fibers separate. Thereafter, a progressive

10. Howes, E. L.; Sooy, J. W., and Harvey, S. C.: The Healing of Wounds as Determined by Their Tensile Strength, *J. A. M. A.* **92**:42 (Jan. 5) 1929.

11. Howes, E. L.: The Strength of Wounds Sutured with Catgut and Silk, *Surg., Gynec. & Obst.* **57**:309 (Sept.) 1933.

12. Whipple, A. O.: The Use of Silk in the Repair of Clean Wounds, *Ann. Surg.* **98**:662 (Oct.) 1933.

13. Howes, E. L., and Harvey, S. C.: Tissue Response to Catgut Absorption, Silk and Wound Healing, *Internat. J. Med. & Surg.* **43**:225 (April) 1930.

diminution in the cross-section of the strand occurs, with complete absorption from the fourth to the sixth day. With chromic catgut there is less swelling of the strand, and absorption is delayed. During the regenerative period, after the first five days, fibroblasts proliferate at the periphery of the suture and occasionally in its interstices.

What I have just described holds true for healing under ideal conditions. Hemorrhage, extensive necrosis of traumatized cells and infection all hasten absorption of the gut and prolong healing of the wound. The regenerative phase of fibroplasia is dependent on the antecedent exudative phase, and if this initial period is prolonged so too will be the stage of actual healing of the wound. As a result of their experiments, Howes and Harvey recommended the use of gut of small size, such as no. 0, twenty day chromic gut, because such a strand will last through the period of healing and be absorbed shortly after healing is complete and because, owing to the smallness of the size, minimal trauma will be incurred and a minimal amount of foreign protein in the form of collagen will be left in the tissues. In addition, the limitations of the tensile strength of the smaller-sized catgut will prevent the unnecessary strangulation of tissue beyond the point of apposition, an abuse which a strand of larger size might easily permit. These workers calculated the various holding strengths of catgut per se in tissues. The holding strength of a stitch in fascia, the only tissue of sufficient density to resist the cutting power of a suture, varies from 7 to 8½ pounds (3.2 to 3.9 Kg.). On the other hand, the holding strength of a strand of no. 0 catgut is 9 pounds (4.1 Kg.). Thus, before the strand of catgut will break, it will tear through the tissue.

#### STUDY OF INTRA-ABDOMINAL PRESSURE

With the aforementioned conception of healing in wounds and the fate of suture material in vivo, a consideration of the important, yet often overlooked, factor of intra-abdominal pressure is in order. The abdominal cavity really represents the interior of a muscular bag. Externally, there is the atmospheric pressure of 15 pounds per square inch, while within the peritoneal cavity three factors—gravity, variations in the omental and mesenteric deposits of fat and variations in the size of the viscera—play their rôles. In an illuminating chapter Livingston<sup>14</sup> reported the results of a study of variations in pressure within the abdomen. In contrast to the negativity of intrathoracic pressure, the general intra-abdominal pressure practically equals that of the atmosphere. Pressures within and without regulate the configuration of the abdominal wall.

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14. Livingston, E. M.: *Pressure Variations Within the Abdomen: A Clinical Study of the Abdominal Cavity and Peritoneum*, New York, Paul B. Hoeber, Inc., 1932.

Each abdominal viscus has an intraluminary pressure of its own. Hence, the need of an intravisceral and an intra-abdominal balance of pressures. The ingestion of a heavy meal eventuates in an altered abdominal pressure, with the need of loosening the constricting apparel. Livingston pointed out the existence of an entero-abdominal reflex, which in this case resulted in relaxation of the abdominal wall, compensating for the increased intraluminary pressure. The storage of fat intra-abdominally in the mesenteric ligaments and extraperitoneal spaces represents nature's "buffer" to strengthen natural supports. Atonicity of viscera is a consequence of marked depletion of such fatty stores.

Clinically, the starvation and cachexia produced by a malignant condition result in the scaphoid abdomen, and, secondarily, the loss of fat is accompanied by a compensating atonic dilatation of the hollow viscera which accounts for the digestive and asthenic symptoms following in the wake of wasting illnesses. In this condition the anterior abdominal wall is passively driven inward by a greater external pressure. On the other hand, an increase in intra-abdominal pressure is responsible for the protuberance seen in the presence of obesity, ascites and the distention of intestinal obstruction.

The abdominal musculature likewise exhibits tonicity, and with the synchronous contraction of the muscular sac which forms the wall of the abdominal cavity, as in coughing, defecation or parturition, a temporary increase in pressure is produced. These groups of muscles can act synergistically or antagonistically. Variations in abdominal pressure are also produced by the thoracic, and especially by the abdominal, type of respiration.

I have taken the liberty to dwell at length on the healing of wounds, on the use of catgut and on intra-abdominal pressure as a premise to my contention that all three factors are closely interwoven in the production of disruptions of abdominal wounds. As has been shown, it is a rare case which does not show a constant source in a persistent or explosive type of increased abdominal pressure. Coughing, hiccup and retching, coupled with distention, were almost universal in this series of cases. Add to this disruptive force a point of lowered resistance, as represented in the laparotomy wound, and the sum spells trouble if the suture material, the healing of the wound or the technic of closure is inadequate.

Coffey<sup>15</sup> showed that, contrary to popular belief, the strong aponeurotic layers enclosing or forming terminal attachments for the muscles of the anterior abdominal wall are but slightly elastic under an ordinarily acute strain. He pointed out that the equilibrium of normal

15. Coffey, R. C.: Intravisceral and Intra-Abdominal Pressure, J. A. M. A. 69:683 (Sept. 1) 1917.

intra-abdominal pressure is established by the intermittent expulsion of the liquid and gaseous visceral contents. However, it must be remembered that postoperatively, especially after general anesthesia, this safety-valve effect is often temporarily upset. Likewise, the entero-abdominal reflex, the regulating mechanism previously cited, is involved. Consider, then, the postoperative status in a case of laparotomy in which there is a clinically stormy course. Owing to operative trauma, the abdominal wall is splinted. Within the abdominal cavity a distended stomach or dilated intestinal loops produce increased pressure. Add to this condition spasmodic, forceful muscular contractions resulting from coughing, vomiting or expulsive efforts, and the strain on a weak operative wound might easily be sufficient to cause dehiscence.

Definite proof exists that the intra-abdominal pressure can often rise to such a level as to transmit considerable force to the anterior abdominal wall. Sporadic cases of spontaneous rupture of the rectus abdominis muscle, subsequent to violent contractions and without external violence, have been reported. Hume,<sup>16</sup> in discussing the etiology of nontraumatic acquired hernias, cited the important rôle played by intra-abdominal pressure in the actual production of herniation. He stated that during violent muscular effort the intra-abdominal pressure may rise to 100 or 150 mm. of mercury, owing partly to diaphragmatic descent but chiefly to the contraction of the anterior and lateral abdominal muscles, especially the transversalis abdominis.

Recently, Murphy and Mengert<sup>17</sup> carried out a study of intra-abdominal pressures created by voluntary muscular effort and measured by a distended balloon in the vagina. While this investigation was carried out as a study of the etiology of prolapse and of the relations of pressure in labor, these workers observed that the manometric column of mercury was set into simple rhythmic vibrations, with the column reaching a much higher level on the first upswing during sudden, sharp abdominal contractions, than when the muscular contraction was slow. Other workers have measured intra-abdominal pressure by inserting a tube in the rectum or a balloon in the esophagus or stomach, by means of a bell jar with a rubber diaphragm placed on the abdomen or even with a cannula penetrating the abdominal wall into the peritoneal cavity.

Clinically, this increase in pressure, uncompensated for by normal physiologic reflexes, produces both subjective and objective signs and symptoms. There is present a visible and palpable abdominal protuberance, and the patient complains of an oppressive type of pain.

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16. Hume, J. B.: Diaphragmatic Hernia, *Brit. J. Surg.* **19**:527 (April) 1932.

17. Murphy, D. P., and Mengert, W. F.: Intra-Abdominal Pressures Created by Voluntary Muscular Effort, *Surg., Gynec. & Obst.* **57**:487 (Oct.) 1933.

The lowering of this pathologically increased pressure by such therapeutic measures as the passage of the Levine tube in cases of acute gastric dilatation, an enterostomy in cases of intestinal obstruction or the effective use of the extract of the posterior lobe of the hypophysis or of spinal anesthesia in cases of paralytic ileus is attended by almost immediate relief to the patient. I have observed that patients, immediately after the disruption of their abdominal wounds, have a feeling of well-being and relief from severe abdominal discomfort. The explanation seems to be that there is an immediate release of intra-abdominal pressure which was created by intravisceral distention. Persistent coughing, with its resultant strain on the abdominal wall, produces sudden increases in intra-abdominal pressure which may easily throw an unbearable strain on the fresh suture line.

#### CLINICAL TYPES SUSCEPTIBLE TO DISRUPTION

In the light of what has been said concerning abdominal pressures, the various types of subjects in whom abdominal wounds disrupt may be considered. The high percentage present in cases of chronic infection or of a malignant growth with attendant cachexia and anemia is attributed by some investigators to poor regenerative powers of the tissues to promote firm healing, while others attribute the dissolution of wounds to "tissue hunger" and the resultant hasty digestion of catgut. There is, in my opinion, one characteristic finding in cachectic patients, no matter what the cause, and that is depletion of the stores of fat, both in the abdomen and elsewhere. The viscera are in an atonic state, and the muscular abdominal sac has little, if any, fatty "buffer" layer which might normally absorb or diffuse a sudden or constant propulsive force arising intra-abdominally from cough, distention or vomiting. A similar situation holds in the cases of hypertrophic pyloric stenosis, a condition in which, according to some observers, disruption of wounds is relatively frequent.

Conversely, the markedly obese patient also presents a problem as far as disruption is concerned. Here, if my assumptions are correct, there is an undue increase in intra-abdominal pressure due to an abnormal deposition of fat, both in the abdominal wall and in the visceral mesenteries and omentum. These patients are poor subjects for anesthesia and are susceptible to respiratory complications. Closure of the abdomen at the termination of an operation is often technically difficult and attended with tearing of the sutures. No better example of such a situation and its remedy is seen than in the case of a large ventral hernia in an obese person, which would defy the surgical ability of a master. Yet, if such a patient is placed on a rigid dietary regimen resulting in appreciable loss of weight, the later repair, closure and postoperative course are uneventful.



From this line of reasoning it must be conceded that the sutured incised wound in the anterior abdominal wall is subjected in a stormy postoperative course to many sudden or constant stresses and strains. This is especially true of wounds in the epigastrium, in which separation of the costal arch with each respiration exerts a lateral pull on the attached muscles and the suture line. Furthermore, the rectus muscles widen and are thinned toward their costal insertions, providing a point of anatomic weakness. According to Howes and Harvey, the suture loses 50 per cent of its strength when the wound has obtained 50 per cent of its maximum strength. This holds true in a normal case. Excessive oozing or necrosis in the wound and a mild infection would admittedly delay healing and increase the rate of absorption of catgut. A slipped knot, the tearing of a frayed strand of catgut, the cutting through of the suture or the strangulation of the sutured tissue would all present points of lowered resistance, easily giving way under an undue strain.

Ries<sup>2</sup> reported 2 cases in which the snapping of the catgut, after it had been used to close a wound, was audible. These accidents, by fortuitous circumstances, were recognized and rectified. In 1 of the cases the patient stated that he "felt something snap." In several of the cases of disruption of abdominal wounds which I have personally observed, catgut in varying lengths was noted in the wounds. The frayed ends of several of the pieces suggested the possibility that the strand of catgut gave way under strain. This has already been alluded to in commenting on the incidence of 6 disruptions in a period of two weeks.

#### PROBLEM OF SUTURE MATERIAL

This brings one to a vital point in the use of suture material, especially of catgut. Despite efforts of the committee on Catgut Standards of the American Medical Association, no agreement has been reached among manufacturers on a standard test for catgut. As a result surgeons must depend on the statements of the various producers as to the quality of their products. Some firms judge the absorbability and tensile strength by experimentation with animals and others by tests *in vitro* with proteolytic enzymes; still others use the chromicizing process for regulation of the absorbability. Obviously, standardization is necessary.

Kraissl and Meleney<sup>18</sup> recently devised an apparatus for testing the tensile strength of strands of catgut against the digestive action of a standard solution of trypsin. They found a variation in the rates of digestion of various brands of catgut of both native and foreign

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18. Kraissl, C. J., and Meleney, F. L.: A Method for Determining the Time of Catgut Digestion in Vitro, *Surg., Gynec. & Obst.* 59:161 (Aug.) 1934.

manufacturers. These workers were of the opinion that the problem can be solved only by analysis of the catgut in vivo and in vitro—hence the presentation of their accurately controlled test tube method adapted to standardization. Misleading statements by manufacturers were cited in which a certain brand of catgut was said to hold tissues for ten, twenty or forty days, while another brand was described as being able to resist complete absorption for ten, twenty or forty days. I have already shown that the benefits of catgut are lost long before it is completely absorbed.

Specialized technics and usages of suture material have been developed by some operators with uniformly good results, as indicated by their reports. Colp, noting the tendency of median epigastric incisions to disrupt, frequently used through-and-through sutures of braided silk, which were removed on the fourteenth day. By this altered method disruption of this particular type of incision was practically eradicated. Kennedy,<sup>19</sup> drawing on the combined surgical experiences of himself and his predecessor, Dr. Joseph Price, during fifty-six years, reported that not a single disruption of an abdominal wound occurred with the use of through-and-through silkworm-gut sutures. In the technic developed by Price and continued by himself, Kennedy uses no absorbable suture material in his abdominal wounds. In contrast to the method and results of Kennedy is the equally impressive statement by Baldwin<sup>20</sup> that he performed 16,465 laparotomies without a dehiscence. He used no. 2 chromic catgut throughout in the closure of the layers of peritoneum, muscle, fascia and skin and silkworm gut for stay sutures.

Freeman<sup>21</sup> propounded an explanation for the causation of disruptions which has many adherents. In his opinion the primary cause lies in the inadequate closure of peritoneum with resultant omental protrusion through such a gap. Subsequently, he stated, the omental wedge becomes edematous and with the accompanying serous exudate produces separation of tissues which only needs the strain of coughing or vomiting to precipitate a dehiscence.

Experimentally, Freeman performed laparotomies on 15 dogs, purposely closing the wounds with a tongue of omentum lying between the edges of the layer of split muscle. He reported a swelling of the omental wedge and the production of a lymphlike fluid but no actual disruption of the wound. Certainly, the suture material served its purpose well in these experiments, in which intentional defects in the muscles

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19. Kennedy, J. W.: *Tragedies of the Abdominal Incision*, *Am. J. Surg.* **25**:512 (Sept.) 1934.

20. Baldwin, J. F.: *Disruption of Abdominal Wounds*, *Am. J. Surg.* **25**:7 (July) 1934.

21. Freeman, L.: *The Cause of Post-Operative Rupture of Abdominal Incisions*, *Arch. Surg.* **14**:600 (Feb.) 1927.

were present together with the natural activity of the dogs. These results, it seems to me, considerably weaken the tenability of Freeman's theory of the omental wedge. The late Dr. Polak,<sup>22</sup> who had seen 11 disruptions in thirty-five years of practice, believed that the accident began before the patient left the operating table, and he attributed the separation to a straining effort, as from coughing, followed by a break in the peritoneal suture.

#### BASIC ETIOLOGIC FACTOR

To my mind, the basic etiologic factor in the disruption of wounds rests in the too frequent failure of the suture material, usually catgut, to hold an incised wound of the abdominal wall beyond the point of safety in the healing of the wound. Some cases may have their beginning in the manner described by Polak. I have already mentioned the cases of Ries, who actually heard the snapping of the suture. Many disruptions, I believe, occur later as the result of the inability of the suture—whether it is of inferior quality or of inadequate tensile strength or whether it is too rapidly absorbed or is misused by the operator—to withstand either a single or a long continued assault from an abnormally elevated intra-abdominal pressure during a stormy postoperative period, before the healing wound has acquired enough tensile strength to combat an unusual disruptive force.

In surveying the conclusions of the many surgeons who have investigated the problem of disruption of wounds, one is impressed with the variability in their respective operative technics and with the multiplicity of conflicting "modifications" which they believe will prevent the catastrophe. Kennedy, in recounting his continued success with interrupted through-and-through silkworm-gut sutures, recommended the omission of all absorbable sutures, especially in the closure of wounds in layers. On the other hand, Baldwin performed 16,465 laparotomies without a single dehiscence, using chromic catgut throughout. The latter author particularly emphasized the use of the binder throughout the postoperative period and convalescence, while other operators use it sparingly, or not at all, without sequelae. Another operator was of the opinion that his success might be due to the use of plain catgut throughout, to the exclusion of chromic gut, which is more irritating to the tissues. However, the majority of laparotomies were performed by this operator, with the patient under spinal anesthesia, with its admittedly diminished incidence of complications that tend to increase intra-abdominal pressure. Similarly, the champions of the tension suture were answered by Colp in his report on the use of these sutures in less than a

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22. Polak, J. O., in discussion on Horner, D. A.: Postcesarean Bursting of Abdominal Wounds, *J. A. M. A.* **93**:1126 (Oct. 12) 1929.

dozen cases in a series of 2,750 laparotomies. He credited the elimination of the sutures with the paucity of liquefactive necroses and deep stitch abscesses.

I can think of no better way of discussing the prophylaxis of disruption of wounds than to present a composite statement of the existing opinions of the surgical<sup>11</sup> "Do's and Dont's" in the conduct of an elective laparotomy. Preoperatively, dehydration, malnutrition, anemia, obesity and the diabetic state should be effectively treated when present. At operation, needless to say, one must exercise strict aseptic technic, minimal trauma in the cutting, clamping and retracting of tissues, complete hemostasis and accurate approximation of the severed layers of tissue. Freeman stressed the need for thoroughness in the peritoneal closure, a prime requisite for which is good relaxation. Hence, the necessity of continuing with a sufficient depth of anesthesia to permit closure of the deep layer as well as the more superficial reenforcing layers.

In suturing the posterior sheath and peritoneum care must be taken not to pull the strand too tightly, for it is an easy matter to tear through the transversely running fibers of the tissue. A similar occurrence follows a closure made difficult, if not impossible, by a straining, half-anesthetized patient. Tying knots too tightly or laying down a continuous layer of sutures under too much tension only results in strangulation, necrosis of the tissue and final giving way of the suture. All that is desired is coaptation. Equally destructive is the insecurely tied knot which gives way at the least strain or test of its holding power. Heyd and Lahey have each recommended the suturing of the split muscle, thus obliterating dead space, combating possible infection and adding to the strength of the closure.

The care of suture material is of great import. Dry and brittle catgut should not be used as it comes from the tube, nor should the strand needlessly suffer injury by application of clamps or by faulty laying down of knots. Drains should be used sparingly, especially when left in the peritoneal cavity. The exposure of the wound proper to digestive ferments should be avoided if possible. Tension sutures are most effective when placed with lateral bolt or button support. The circularly tied suture is liable to cut through the tissue enclosed by it and thus do more harm than good. The success established by Kennedy in the sole use of through-and-through nonabsorbable sutures brings up the question of whether the apposition of tissue in mass is not more effective and practical than the closure by anatomic layers, in which multiple small bites of tissue are taken. Absorbable material when used should be of small size and proved quality, and preferably chromicized.

Postoperatively, the binder should be used as a routine. Its benefits overbalance its disadvantages. Everything possible should be done to

combat undue restlessness, vomiting, coughing, hiccup and distention. In this connection one should consider the question of the selection of the anesthetic in cases that appear to promise trouble. Gastric lavages should be performed as indicated by passing the Levine tube transnasally. This method avoids the usual retching and struggle that attend the passage of a regular stomach tube. With the simple method of lavage available, it would seem that autolavage, which demands more effort on the part of the patient, should be discarded. Sutures, especially tension sutures, should not be removed by rote. It would be folly to remove a valuable restraining agent in a patient who is still passing through a turbulent postoperative period. Nonabsorbable tension sutures should remain in situ for from twelve to fourteen days, the time thus extending beyond the period of weakness in the healing of the wound.

#### CONCLUSION

A consecutive series of 1,560 laparotomies has been studied in an effort to arrive at a clearer understanding of the mechanism of the production of disruption in abdominal wounds. What has been gleaned from this study in the way of figures and facts has been duly recorded and analyzed. I have chosen to dwell on the broader aspects of the problem, elaborating on the phases of the healing of wounds, the usage and fate of catgut and a consideration of intra-abdominal variations in pressure. Only by a study of these fundamental elements in the repair of an incised wound of the abdominal wall could conclusions be reached. Parenthetically, it might be added that too little consideration has been given to the study of intra-abdominal pressure, practically as well as theoretically, for few of the standard texts on physiology even mention the subject.

I believe that most cases of disruption of abdominal wounds represent a failure of the suture line to hold—whether it is due to the suture material or to abuse—in the face of undue intra-abdominal pressure. Without the added factor of excessive abdominal pressure, many inherently weak wounds may escape disruption. The solution lies in the minimizing of the disruptive forces and in the more prevalent use of nonabsorbable, removable sutures, the effect of which is to tide a healing wound over its early period of weakness. I agree with Freeman that the emphasis by some writers on the etiologic importance of age, sex, seasonal incidence, the primary illness and allergic phenomena is merely “begging the question.” It is believed that the newly awakened interest in the subject will lead to a revaluation of the present accepted methods of the closure of wounds and to a closer scrutiny of the efficacy of absorbable suture material and of the surgeon’s security in using it in the closure of a laparotomy wound.

# SO-CALLED "LIVER DEATH"

A CLINICAL AND EXPERIMENTAL STUDY

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The conception of disease of the biliary tract which includes in its compass involvements of the liver as well as of the gallbladder is of relatively recent origin. Indeed, it dates from the observation of Reimann of the Lankenau Clinic, in 1917, that hepatitis of some degree is a constant accompaniment of cholecystitis of any degree. That observation was confirmed experimentally by Graham, of St. Louis, in the following year, and since then notable work has been done on the association of disease of the liver with disease of the biliary tract, particularly by Heyd and Martin of New York and by Judd and Walters of the Mayo Clinic, while Riemann's and Graham's further studies have continued the promise of their early investigations. Today, even though all surgeons may not be willing to grant, as many claim, that hepatitis actually precedes cholecystitis in some, if not in all, cases, they accept without question the association of the two diseases, and they comprehend, practically as well as theoretically, that the health and the safety of the patient following operation for biliary tract disease depend largely on the state of the liver.

In 1890, in one of the earliest publications on the subject, Courvoisier reported a mortality of 16 per cent following operations on the biliary tract. In 1934 Heuer<sup>1</sup> reported a mortality of 6.6 per cent in more than 35,000 operations. And Graham,<sup>2</sup> speaking for himself and his associates, recently reported a mortality of 0.4 per cent following simple cholecystectomy and of 2 per cent following operations on the common bile duct. It is not too much to say that this astonishing reduction in the collective and individual surgical mortality is due in no small part to the surgeon's comprehension of the inseparable association of the liver and the gallbladder in cases of disease of the biliary tract, plus, we think it is only fair to add, the commendable habit of modern physicians

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1. Heuer, G. J.: *The Factors Leading to Death in Operations upon the Gallbladder and Bile-Ducts*, Ann. Surg. 99:881 (June) 1934.

2. Graham, E. A.: *Lowering the Mortality After Operations on the Biliary Tract*, Illinois M. J. 60:196 (Sept.) 1931.

of analyzing their own results, especially their failures. An analysis of this sort, it seems to us, is particularly important in cases of disease of the biliary tract because operation for this particular condition in the majority of cases is done by election, that is, it is done by choice to restore health rather than as an emergency measure to save life.

As soon as the factors of mortality following operations on the biliary tract began to be carefully analyzed, it was promptly realized that they fell—and still fall—into certain definite groupings. The immediate factors, if we may so express ourselves, include hemorrhage, shock and embolism, while the delayed factors include peritonitis and complications of the respiratory tract. But in a certain group of cases, the significance of which Charles Gordon Heyd was apparently the first to comprehend, none of these factors operate. The patients, for the most part, are not desperately ill; the majority of them seem to present an unusually good surgical risk. Many of them die too promptly for the death to be explained on an infectious basis but too late for surgical shock to play any part, while a certain group in whom death is deferred exhibit no clinical evidence of infection or pneumonia. Furthermore, autopsy, the court of last resort in medicine, throws no light on the problem, for it eliminates all the usual causes of postoperative death.

Spurred thereto by his own experience and by his comprehension of the significance of this train of events, Heyd,<sup>3</sup> in continuation of his valuable studies on the liver in its relation to abdominal infection, divided the fatal cases into three general groups in which the course is as follows:

In group 1 the patient is frequently obese and gives a history of long-standing disease of the biliary tract. He is a good risk and has no organic defects that can be demonstrated; cholecystectomy, frequently in combination with appendectomy, is easily done. There is, however, a delayed recovery from the anesthetic; a semicomatose state ensues, which is followed by carphology, subsultus tendinum, coma, and death within from twenty-four to forty-eight hours. Hyperpyrexia is the outstanding symptom in this group.

In group 2 the patient has jaundice, and there is often a history of previous operation on the biliary tract. He is not so satisfactory a risk as the patient in group 1, but he cannot be considered a poor one. Operation, which may range from cholecystostomy to choledochostomy, is not extraordinarily difficult. Convalescence is satisfactory for from thirty-six to forty-eight hours. Then the patient becomes irritable and nervous; there is pronounced and abrupt vasomotor collapse, and death ensues from twenty-four to forty-eight hours later. Hyperpyrexia is again a feature.

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3. Heyd, C. G.: Liver and Its Relation to Chronic Abdominal Infection, *Ann. Surg.* 79:55 (Jan.) 1924.

In group 3 the patient exhibits calculous cholangitis and sometimes pancreatitis, and more rarely there is a pancreatic malignant disease. The seriousness of his condition is realized, but he is properly prepared, and he does not, all things considered, present a bad risk. Operation may be cholecystostomy, choledochostomy and cholecystenterostomy or the creation of an external biliary fistula. Convalescence is satisfactory, or even good, for the first five or six days; the jaundice decreases, and the patient is considered on the road to recovery, when suddenly somnolence ensues, which passes into coma, and death is only a question of time. In this group of cases a deferred renal factor is apparent, beginning as oliguria and frequently progressing to complete anuria, in contrast to the first two groups in which the most striking and dramatic feature of the clinical course is the sharp and progressive elevation of temperature, which, once the upward course has begun, continues without remission until it reaches 106 F. and higher.

Heyd's<sup>3</sup> report, the substance of which we have roughly summarized, was made in 1924, and Cave,<sup>4</sup> two years later, reported 3 cases of a similar nature in a group of 35 in which death followed operation on the biliary tract, all of which seem to belong in group 1. Stanton,<sup>5</sup> in 1930, reported 15 fatal cases of the same type as Heyd's group 1, the data being collected from 100 hospital records which he studied personally. He mentioned Cave's cases, but he seems to have overlooked Heyd's, probably because the title of the paper was misleading. Since then similar cases have been reported and studied by Behrend, Connell, Eiss, Graham, Helwig, Schutz and Kuhn, Petren, Ravdin, Sharples,<sup>6</sup> Wilensky and Colp, and one or two other authors, the total number amounting, in the collective study made by Heuer, to about 95 cases.

But the problem of the so-called "liver death" was soon to assume a wider significance, and not the least interesting feature of it is the manner in which the significance of previous observations on apparently unrelated or at least irrelevant subjects is coming to be realized. Thus in 1927 Furtwaengler, from Clairmont's Clinic in Zurich, introduced an entirely new element into the situation by reporting the case of a young woman who, after an automobile accident, presented precisely the same fatal course as the patients in Heyd's group 3. Helwig and Orr,<sup>7</sup> in

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4. Cave, H. W.: Dangers Incident to Cholecystectomy, *Ann. Surg.* **84**:371 (Sept.) 1926.

5. Stanton, E. M.: Immediate Causes of Death Following Operations on Gallbladder and Ducts, *Am. J. Surg.* **8**:1026 (May) 1930.

6. Sharples, C. W.: Liver Deaths Following Operation on Biliary Tract, *West. J. Surg.* **42**:337 (June) 1934.

7. Helwig, F., and Orr, T. G.: Traumatic Necrosis of the Liver with Extensive Retention of Creatinine and High Grade Nephrosis, *Arch. Surg.* **24**:136 (Jan.) 1932.



1932, reported a similar case, but they, as well as Furtwaengler, overlooked the fact that in Stanton's report just such a case had been reported, although this patient was referable to Heyd's group 1. Stanton gave no postmortem observations, but in Furtwaengler's and in Helwig and Orr's cases autopsy revealed, in addition to the expected traumatic necrosis of the liver, high grade bilateral necrosis of the cortex of both kidneys.

Willard Bartlett Jr.,<sup>8</sup> in an extensive paper on the subject of renal complications of infections of the biliary tract, emphasized the renal factor in these cases. The majority of the cases which he reported are not, in our opinion, entirely germane to this discussion, for the reason that in some instances no operation was done while in others the renal disability was demonstrated before operation. He gave, however, an interesting summary of the particular investigations devoted to this aspect of the problem. In 1911, he pointed out, Clairmont and von Haberer, after reporting 5 cases of renal failure following operation on the biliary tract, 3 of which were fatal, attempted to produce anuria experimentally by ligation of the common bile duct; excretion of dye showed some impairment of function, but the experiments were not successful. In the same year Steinthal noted anuria on the fourth day after operation on the common bile duct; autopsy showed acute tubular degeneration of the kidney. He considered that the anesthetic had precipitated the fatal result, there having been a latent renal insufficiency present as a sequela of hepatic damage. In 1921 Staeheli reported a fatal case in which cholecystectomy and choledochostomy had been performed, but we question whether it has any bearing on the subject, since autopsy revealed arteriosclerosis of the kidneys. A case of oliguria following cholecystectomy, reported by Kehr and mentioned by Staeheli, presents no such extraneous factor and undoubtedly belongs to the group of cases we are discussing. In 1922 Parham and Walters reported instances of several patients dying of renal insufficiency after operation on the biliary tract, and an extended report on the same subject was made by Wilensky and Colp<sup>9</sup> in 1927. It is impossible to mention, let alone summarize, within the confines of this brief paper the work of Rowntree, Snell and Green and many others along both experimental and clinical lines.

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8. Bartlett, W., Jr.: Renal Complications of Biliary Tract Infections, Surg., Gynec. & Obst. **56**:1080 (June) 1933.

9. Wilensky, A. O., and Colp, R.: Relation of Nitrogen Bodies of the Blood to Surgical Problems in Liver and Biliary Tract Diseases: III. Status of Nitrogen Bodies of Blood in Severe Cases of Biliary Tract Disease, and Its Use in Differentiating a Terminal Hepatic and a Terminal Renal Group of Cases, Arch. Surg. **15**:635 (Oct.) 1927.

But there are still other aspects of the problem. Ravdin,<sup>10</sup> writing in 1929 on the subject of vasodepressor substances in the liver after obstruction of the common bile duct, recalled that Ransahoff, in 1908, endeavored to explain the shocklike states which occasionally supervene after such operations. Connell, in 1931<sup>11</sup> and again in 1934,<sup>12</sup> linked the problem of "liver death" with sudden postoperative death associated with high temperature, cases of which were reported by Gibson, Johnson and Brewer<sup>13</sup> in 1900, Crandon and Ehrenfried<sup>14</sup> in 1912, Moschcowitz<sup>15</sup> in 1916 and Martin<sup>16</sup> in 1928. Reports of 26 such deaths were collected by Cutting<sup>17</sup> in 1931, but he, like all previous writers, endeavored to explain them simply as due to heat strokes, with climatic conditions as the probable underlying cause; the surgical significance of such deaths seems, as we have said, to have been realized first by Connell. Climatic conditions, we might interpolate at this point, would not explain such deaths in New Orleans, where, although long periods of very hot, humid weather are the rule during the summer months, heat stroke as such is an almost unknown accident.

Finally, there is a notable tendency on the part of many recent writers to extend the field of this problem to include not only deaths following operations on the biliary tract and deaths following trauma to the liver but also deaths occurring after such widely different conditions as burns, drug poisoning and intestinal obstruction (Wilensky and Colp). Connell, writing in 1934, definitely retracted the statement which he made in his 1931 paper, that death with hyperpyrexia was noted only after operation on the biliary tract, and we ourselves, as we shall point out later, are in entire accord with his and with Wilensky and Colp's point of view.

It might be well, at this point, to specify the changes which are uniformly noted in these cases at autopsy. In none of them, as we

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10. Ravdin, I. S.: Vasodepressor Substances in the Liver After Obstruction of the Common Duct, *Arch. Surg.* **18**:2191 (May) 1929.

11. Connell, F. G.: Rapid High-Temperature Deaths Following Biliary-Tract Surgery, *Ann. Surg.* **94**:363 (Sept.) 1931.

12. Connell, F. G.: Liver Deaths (So-Called), *Ann. Surg.* **100**:319 (Aug.) 1934.

13. Gibson, C. L.; Johnson, A. B., and Brewer, G. E.: Heat-Stroke as Postoperative Complication, *J. A. M. A.* **35**:1685 (Dec. 29) 1900.

14. Crandon, L. R. G., and Ehrenfried, A.: *Surgical After-Treatment: A Manual of the Conduct of Surgical Convalescence*, ed. 2, Philadelphia, W. B. Saunders Company, 1912.

15. Moschcowitz, A. V.: Post-Operative Heat Stroke, *Surg., Gynec. & Obst.* **23**:443 (Oct.) 1916.

16. Martin, T. M.: Report of Four Cases of Postoperative Heat Stroke, *J. Missouri M. A.* **25**:305 (July) 1928.

17. Cutting, R. A.: Postoperative Heat Stroke, *Am. J. Surg.* **13**:624 (Sept.) 1931.

have said, is there any anatomic or infectious explanation for the death. Indeed, in groups 1 and 2 of Heyd's classification the organs are approximately normal, with the exception of the liver, which shows diffuse toxic changes progressing in some cases to degeneration and actual necrosis; usually the only other abnormality is slight congestion of the kidneys. In group 2, on the other hand, just as in the 2 cases of trauma to the liver reported by Furtwaengler and by Helwig and Orr, there is, in addition to these hepatic changes, a marked degree of renal damage, chiefly tubular degeneration which ranges from granular changes to actual necrosis and sequestration of the cells.

In other words, the cases fall into two distinct clinical and histologic groups. In the first group hyperpyrexia and death soon after operation make up the syndrome, while degenerative changes in the liver form the predominant picture at autopsy. In the second group the clinical picture is one of uremia; death is deferred, and there are postmortem changes of a degenerative character in the kidneys as well as in the liver.

One thing that impressed us immediately in our review of the literature on this subject was the wide disparity of the figures, or, more properly, of the impressions, concerning the incidence of so-called "liver death." The majority of authors have mentioned only isolated cases, but Stanton reported 15 which he was able to locate personally from his study of hospital records, and he stated that he would be willing to transfer to this group several other cases set down under other causes of death, while Connell reported 17 in 1931, to which number he added 8 in 1934. Heuer, on the other hand, in spite of his extensive surgical experience, said that he had never seen a case of cholecystitis without jaundice in which the cause of death could not be explained in some other way. The important consideration, of course, is not the exact incidence of the complication but the fact that it does occur and that when it occurs it is almost invariably fatal. A complication of such actual and potential gravity is clearly worthy of serious investigation, and it was with the idea not only of studying our own cases but of seeking some solution for the whole problem that we undertook this study.

#### CLINICAL DATA

We began our study with an analysis of the last 100 "gallbladder deaths" occurring in the New Orleans Charity Hospital (a separate study of which we shall shortly publish), and we found, to our surprise, that 23 of them, almost 25 per cent, fell into the type under consideration. As a matter of convenience we have chosen to group them as follows:

*Group 1.*—A. Death within forty-eight hours, with hyperpyrexia; 6 cases: The age range of the patients was from 38 to 68 years, with an

average age of 53 years, and 3 were very obese. All of them gave a history of long-standing infection of the biliary tract, but none of them was acutely ill, and all were regarded as presenting a good surgical risk. None of them had jaundice, but 2 were found at operation to have calculi. In 2 instances the operation was done as an emergency measure several days after admission because of an exacerbation of symptoms, but even these patients had some sort of preoperative preparation. Ether anesthesia was used in 5 cases and spinal anesthesia in 1, and the surgical procedures were evenly divided between cholecystectomy and cholecystostomy. In all cases the clinical course corresponded with Heyd's group 1, death within forty-eight hours with rapidly increasing hyperpyrexia, terminating in an axillary temperature of from 105.2 to 107 F., and an associated rising pulse rate.

B. Death within seventy-two hours, with hyperpyrexia; 5 cases: The age range of the patients was from 24 to 58 years, with an average age of 39 years. Two of the patients were obese, but 2 others had lost considerable weight during their illness, a circumstance which the surgeon who performs operations on the biliary tract is inclined to look on with favor. All of them gave a history of chronic infection of many years' duration; 1 had jaundice, 1 had previously undergone cholecystostomy, and at operation 4 were found to have stones. In 1 case the gallbladder was hydropic, and in another case there was marked hepatitis, but the condition of the liver, as in most reported cases, was unfortunately not stated in the majority of the operative records. One operation was done as an emergency measure immediately after admission; the other patients had more or less adequate preoperative preparation. Ether anesthesia was used in 2 cases, spinal anesthesia in 2 and spinal and ether anesthesia in 1; cholecystectomy was done in 4 cases and cholecystostomy in 1. The clinical course was the same in all cases and suggests Heyd's group 1 classification—a fair recovery or an entirely satisfactory recovery for from twenty-four to forty-eight hours and then hyperpyrexia (105 to 107 F. by axilla) but no other notable symptoms except a rising pulse rate. In all these cases the postoperative carbon dioxide-combining power indicated acidosis, ranging from 24 to 38 volumes per cent. In all the cases in this group and in group 1 A in which autopsy was done the picture was the same, i. e., degenerative changes within the liver and some congestion of the kidneys.

C. Fairly normal course for four or five days, then hyperpyrexia and death within twenty-four hours; 2 cases: Both of the patients in this group, who were respectively 23 and 48 years of age, presented a good risk, and although both gave a typical history of long-standing biliary tract disease, only 1 had jaundice and exhibited stones. Ether

anesthesia was used in 1 case, and ethylene and ether in the other, and in both cholecystectomy and appendectomy were done without difficulty. Convalescence was smooth for the first four or five days; then the clinical course described in groups 1 A and 1 B ensued, with a rapidly mounting temperature (to 106 and 107 F. by axilla) and an associated mounting pulse rate. The deferred death naturally introduces the possibility of peritonitis, but there was no clinical or postmortem evidence of this condition. In both cases, however, some renal factor was apparent at the end; in 1 the patient voided only once within the last twenty-six hours of life, the quantity, unfortunately, not being charted, and in the other also the output could not be measured since the patient voided involuntarily "in small amounts," according to the nurse's notation. In 1 case the carbon dioxide-combining power was 42 volumes per cent, and the nonprotein nitrogen content, previously within normal limits, rose to 50 mg. per hundred cubic centimeters of blood at death. In both cases only partial autopsy was permitted, and a histologic examination of the kidneys was not made, but the marked damage to the liver cells previously described was verified microscopically.

*Group 2.*—A. Smooth recovery for from five to ten days, then oliguria, progressing to terminal anuria, with symptoms of uremia but an absence of the hyperpyrexia noted in group 1; 4 cases: The age range of the patients was from 32 to 49 years, with an average of 42.4 years. There was the usual history of infection of the gallbladder, and 2 patients had jaundice and exhibited calculi, although again they were not suspected to present a poor risk. One gallbladder was hydropic, and 1 showed a small patch of gangrene. Ether was used in 1 case, ethylene and local infiltration in 1 and spinal anesthesia in 2. Cholecystectomy was done in 2 cases, and cholecystostomy and choledochostomy in 1 each. In all cases there was at first a smooth recovery and then a turn for the worse ensued; oliguria, progressing to anuria, dominated the picture, and death occurred in what amounted to uremic coma. In all cases there was a rise in the amount of nonprotein nitrogen, and the urine showed albumin and casts. In 2 of these cases, as in the similar cases reported by Helwig and Schutz,<sup>18</sup> postoperative rupture of the wound occurred. In the cases in which autopsy was performed parenchymatous degeneration was found in the liver, accompanied by degeneration, progressing to necrosis, of the convoluted tubules of the kidney.

B. Cardiorespiratory collapse in from sixty to ninety-two hours; 3 cases: There was the usual history of long-standing biliary tract disease; the age range of the patients was from 24 to 52 years, with an average

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18. Helwig, F., and Schutz, C. B.: A Liver Kidney Syndrome, *Surg., Gynec. & Obst.* 55:570 (Nov.) 1932.

age of 44.5 years, and 1 patient was obese. Ether and spinal and splanchnic anesthesia were used, and cholecystectomy was done in all cases. In from sixty to ninety-two hours there occurred marked cardiorespiratory collapse, with clear evidence of vasodepression, and in 1 case there were repeated convulsions. The carbon dioxide-combining power indicated both acidosis and alkalosis (the alkalosis, in our opinion, being explained by the form of therapy employed); it ranged from 22 to 74 volumes per cent, and in the latter case the nonprotein nitrogen content was 74 mg. per hundred cubic centimeters. In another case it was 120 mg. Oliguria was a striking feature in the 2 patients who lived longest. In all of these cases death ensued in from three to six days after collapse had occurred, there being no response to any measures aimed to correct the altered blood chemistry. Postmortem examination, unfortunately, was not permitted in any instance.

When one attempts to analyze these cases it is evident immediately that although clinically and histologically they fall into two distinct groups, there is no obvious common factor to explain the fatality. The age range was very wide, from relative youth to relative old age, so an unsuspected renal lesion is not a reasonable explanation in all cases, for renal lesions of this sort in young persons are most unusual. Death cannot be explained on the basis of anesthesia, for all varieties were used. Some of the patients were obese, but well over half of them were not, and some were thin. The pathologic process was rarely serious enough to make the operation difficult or to cause a bad risk, and although in a few instances technical errors were made, chiefly a leakage of bile, there is not the smallest clinical or autopsy evidence that these accidents played any part in the final catastrophe.

In line with Heyd's suggestion that pancreatic disease is sometimes characterized by this same postoperative syndrome, we investigated the deaths after operation on the pancreas for the last seven years in the Charity Hospital, and while we found no instances of hyperpyrexia we did find 4 cases in which there occurred the sort of deferred death with renal damage which we have been discussing. These cases, for convenience of reference, we shall term group 3.

*Group 3.*—There were 4 cases in this group. The age range of the patients was from 22 to 62 years. Two patients were obese. Operation was performed in 3 cases as an emergency measure immediately after admission, and 1 patient had previously undergone cholecystostomy, but with one exception all of them, as pancreatitis goes, presented a fairly good risk. Spinal analgesia was used in all cases, and the operations included simple exploration, drainage of the pancreas, cholecystostomy and cholecystectomy and appendectomy. The outstanding feature of the clinical course in all instances was deferred oliguria progressing to anuria and associated with typical changes in

the blood chemistry, chiefly a rise in the amount of nonprotein nitrogen, which in 1 case reached 66 mg. per hundred cubic centimeters of blood and in another, 92 mg. Postmortem examination was done in 2 cases and revealed, in addition to the pancreatic disease, degenerative changes in the liver cells and in the tubules of the kidney paralleling the changes described in the cases in which death followed operation on the biliary tract.

Again, in line with the suggestion of Furtwaengler, Helwig and Orr, and Stanton, that trauma to the liver may produce a similar hepatorenal syndrome, we investigated such deaths, including deaths from gunshot wounds of the liver, which occurred over the last seven years in the Charity Hospital, the same period covered in our study of disease of the biliary tract. The cases which presented this syndrome fall into two distinct classifications, corresponding to groups 1 A and 2 A following operation on the biliary tract, and for convenience of discussion we shall term them groups 4 A and 4 B.

*Group 4.—A.* Cases following gunshot wounds (3) and following an automobile accident (1): The age range of the patients was from 8 to 32 years, with an average age of 22.3 years. Exploration under ether anesthesia was done immediately in 3 cases and six days after admission in 1 case, after marked jaundice had developed, as in the case reported by Helwig and Orr. In 3 cases the patient died within from twenty-four to thirty-six hours of the injury, with an axillary temperature of from 105.4 to 108.2 F., while in the fourth case hyperpyrexia promptly followed operation, at which, it should be noted, no trace of peritonitis was detected. These cases were all coroner's cases, and autopsy was not permitted within the hospital.

*B.* Cases in which rupture of the liver occurred as the result of an automobile accident (2): The ages of the patients were 8 and 48 years, respectively. Immediate exploration was done on both, in 1 instance under ethylene anesthesia and in the other under spinal analgesia. The clinical course precisely paralleled that of the patients in group 2 A, who made a smooth recovery immediately following operation on the biliary system but who exhibited deferred uremic symptoms. In 1 case in this group profound jaundice ensued, the icterus index reaching 210. Autopsy in both cases revealed typical degenerative changes within the liver and the kidneys, in 1 instance so extreme as to suggest the pathologic process of acute yellow atrophy.

We were able to locate several other cases following operation on the biliary tract which seemed to fall into one or another of the classifications we have discussed, but we have omitted them from our groupings because other factors which might be open to criticism were present also. In 1 case, for instance, in which operation was performed under spinal analgesia, hemorrhage of a mild—certainly

not of a fatal—degree was an associated phenomenon; death occurred within sixteen hours, with marked hyperpyrexia, and autopsy showed what amounted to acute yellow atrophy of the liver, with tubular degeneration of the kidneys. This patient, it should be added, had previously undergone cholecystostomy. Four other cases were discarded because the element of infection clouded the picture, though in our opinion death occurred too promptly and too typically for it to have played any part in the outcome.

It is evident, then, that after operation on the biliary tract, after operation on the pancreas and after traumatic necrosis of the liver there may occur a typical clinical syndrome in which death occurs promptly, with hyperpyrexia as the outstanding feature, or occurs later, with renal symptoms as the outstanding feature. On the pathologic side, in the first group of cases the postmortem changes are chiefly limited to degenerative changes within the liver, associated with slight congestion of the kidneys, while in the second group the same hepatic changes are present, plus similar degenerative changes within the convoluted tubules of the kidneys. The only marked difference between the deaths following operation on the biliary tract and those following trauma to the liver is, as Helwig and Orr pointed out and as we ourselves have noted, that in the cases in which death follows traumatic necrosis of the liver the degenerative changes within the liver are limited to the traumatized area, whereas in true hepatic disease they are widespread; in both traumatic and pathologic states, however, the damage to the kidneys is widespread.

#### EXPERIMENTAL DATA

Following this clinical study, and with the clinical syndrome clearly in mind, we endeavored to reproduce in experimental animals the clinical and pathologic processes we had observed in human beings, hoping that some explanation might thus be evolved which would fit all cases, those exhibiting only hepatic lesions and those exhibiting both hepatic and renal lesions. These processes we endeavored to reproduce by the following methods:

1. Traumatic necrosis of the liver.
2. Various types of interference with the hepatic and the portal circulation.
3. Obstruction of the biliary tree.
4. Obstruction of the biliary tree with later release of the obstruction.
5. Intraperitoneal and intravenous injection of extracts made from the livers of animals in which the biliary tree had been obstructed and later released.
6. Injection of the same extracts of animals in which previous damage to the liver had been produced by the use of a carbon tetrachloride mixture.
7. Intraperitoneal injection with the extract of the liver of a patient who died with hyperpyrexia thirty-two hours after cholecystectomy.



8. Implantation of normal liver into the peritoneal cavity, as previously done by Mason, Dragstedt, and Andrews and Hrdina.<sup>19</sup>

9. Intraperitoneal injection of extracts of normal liver, as done by the same authors.

10. Intravenous injection of the same extracts.

It would be well to state at this point the conditions under which all of these experiments were performed. We selected animals which were grossly normal and which had normal renal function as proved by urinalysis and by studies of the blood chemistry. We also measured the twenty-four hour output of urine for several days prior to the experiment to obtain the average for each animal.

All the experiments, furthermore, were conducted under strictly aseptic precautions, and the liver extracts were made under the same conditions. Anesthesia was variously a light ether narcosis or local analgesia for all the experiments except series 2, in which veterinary pentobarbital sodium was used. This anesthetic we found to produce a most satisfactory narcosis when given in the proper dosage, and we observed no evidence of toxicity following its use. Inhalation anesthesia with ether was given in the minimum degree, and while we recognized the possible toxic factor thus introduced, we felt that ether must be used in our experiments if we were actually to parallel the clinical conditions present in these cases.

1. *Traumatic Necrosis of the Liver.*—The abdomen was opened through an upper right rectus incision, and various manual and instrumental methods were employed to traumatize the liver substance without fracture of the capsule. If the capsule was broken and intraperitoneal hemorrhage occurred, the animal was discarded. In all cases there was evidence of more or less shock after the injury, and in a few cases death followed promptly. In the animals which survived there were noted a diminution in the twenty-four hour output of urine, with the appearance of albumin, casts and red blood cells, and an insignificant rise in the amount of blood nitrogen. Within from seven to ten days after the injury these symptoms disappeared, and the animal seemed normal in all respects.

Evidently sufficient hepatic damage cannot be achieved by this method to reproduce the traumatic or pathologic renal damage responsible for the hepatorenal syndrome. Helwig and Schutz,<sup>18</sup> in a series of similar experiments on dogs and rabbits, reported the same difficulties and the same absence of positive renal signs in the animals which survived the immediate period of shock.

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19. Andrews, E., and Hrdina, L.: Cause of Death in Liver Autolysis. *Surg., Gynec. & Obst.* 52:61 (Jan.) 1931.

2. *Various Types of Interference with the Hepatic and the Portal Circulation.*—In line with the suggestion made by Ravdin, Behrend and others that "liver deaths" may be due to accidental ligation at operation of some part of the blood supply of the liver, normal or anomalous, we ligated, at various times, the hepatic artery, one branch of the portal vein, one branch of the portal vein and the hepatic artery and both branches of the portal vein. These experiments have given us some very interesting results not germane to this particular discussion, which have been reported in another paper,<sup>19a</sup> but they threw no light on this problem. The animals in which complete occlusion of the portal vein was done at one sitting died promptly, within from thirty minutes to three hours, with the exception of 1 dog which was kept alive for five hours by infusions of dextrose. In all of the animals which survived there was some immediate evidence of shock, but there were no changes in the urinary findings or the blood chemistry to indicate that interference with the portal or the hepatic circulation had reproduced in any degree the pathologic changes of the hepatorenal syndrome. Helwig and Schutz,<sup>18</sup> experimenting with temporary ligation of the hepatic artery in rabbits, achieved positive results in only 1 case. In this instance there resulted an extensive focal coagulation necrosis of the liver and a state of almost complete anuria associated with albumin, casts and red blood cells in the urine and a rise in the nonprotein nitrogen content to 55 mg. per hundred cubic centimeters. These same authors, in another paper<sup>20</sup> written with H. P. Kuhn, mentioned Gunderman's experimental production of uremia by ligation of the hepatic artery.

3. *Obstruction of the Biliary Tree.*—In some animals the common bile duct was ligated and divided, and the distal end was buried; in others the same procedure was combined with cholecystectomy, with the idea of securing a more rapid rise in pressure. In all cases, it should be said, anomalies of the biliary passages were searched for and due account was taken of those found. Jaundice, usually very deep, promptly developed in all the animals so treated, but the urinary findings were practically unaltered, as was the blood chemistry. Such deaths as did occur were quite clearly due to infection, and there was no evidence in any case of the changes in the liver or kidney that we had been seeking to produce.

4. *Obstruction of the Biliary Tree with Later Release of the Obstruction.*—In the animals which survived the obstruction of the biliary tree

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19a. Boyce, F. F.; Lampert, R., and McFetridge, E. M.: Occlusion of the Portal Vein: An Experimental Study with Its Clinical Application. *J. Lab. & Clin. Med.* 20:935 (June) 1935.

20. Schutz, C. B.; Helwig, F. C., and Kuhn, H. P.: A Contribution to the Study of So-Called Liver Death. *J. A. M. A.* 99:633 (Aug. 20) 1932.

just described and in which there was no evidence of infection, the obstruction was continued for from twelve to twenty days. Then the abdomen was reopened and the obstruction was released by the creation of an external biliary fistula. For this purpose we used a specially devised cannula, stopped by a screw, by the removal and reinsertion of which we hoped to be able to release and recreate the obstruction at our pleasure. We were unable to carry out this plan, however, because of the mechanical difficulty of keeping the dogs from pulling at the cannulas or catching them on the wire network of their cages.

In all cases the clinical course was the same following the release of the obstruction. There was a prompt decrease in the jaundice, associated with increasing listlessness, anorexia, (without symptoms related to the gastro-intestinal tract) and death within from seventy-two to ninety-six hours of those animals which were not killed when their state was terminal. There were also noted oliguria which promptly progressed to anuria, together with the appearance of albumin, casts and red blood cells in the urine, and a rise in the amount of nonprotein nitrogen, which in 5 cases was variously 72, 81, 93, 105 and 171 mg. In 3 of these cases (81, 93 and 105 mg.) the estimations were made the day before death, and through a most unfortunate error the final determinations, which we are sure, in the light of the clinical course and the autopsy observations, would have mounted appreciably, were incorrectly made and had to be discarded.

In all cases examination of the abdomen after death showed no evidence of peritonitis. Only faint traces of jaundice were apparent. The liver was greenish and slightly enlarged, and there was no gross evidence of the accumulation of bile.

Histologic examination of the liver and kidneys revealed precisely the same changes noted in human subjects following "liver-kidney deaths." In the liver the periportal areas showed no significant changes; there was no evidence of cholangitis or biliary stasis, but there were central areas of degeneration, with vacuolation and fragmentation of the nuclei of the liver cells. In some cases there was noted the deposition of a peculiar, homogeneous, red-staining material the nature of which, although not clear from the hematoxylin and eosin stain, was undoubtedly hyaline. In other cases the central area of the liver showed actual necrosis of the liver cells, without significant change in the architecture of the portal fields. In all cases the kidneys showed engorgement of the blood vessels, interstitial hemorrhage and tubular degeneration.

It seems quite clear from this group of experiments that the renal changes found at autopsy in such cases, whether clinical or experimental, are the end-result not of the obstruction of the biliary tract (for we found no such changes in those cases in which only obstruction was

produced) but of the release of the obstruction. Hepatic changes of some degree are, as we have said, the constant accompaniment of all degrees of cholecystitis, but whether the extreme hepatic changes noted in such cases are the result of the original obstruction or of the release of the original obstruction we have not yet determined. There seems no question, however, that they are aggravated by the surgical procedure which releases the obstruction and that the renal changes are positively precipitated by it.

5. *Intraperitoneal and Intravenous Injection of Extracts Made from the Livers of Animals in Which the Biliary Tree Had Been Obstructed and Later Released.*—The livers of the animals so treated which had died or which had been killed when their condition was terminal were removed and run through a small grinding machine, under strict aseptic precautions. The substance thus obtained was extracted with physiologic solution of sodium chloride, with sterile distilled water and with alcohol and the extracts injected into normal animals intraperitoneally and intravenously. The dog given the alcohol extract intravenously died promptly, undoubtedly as the result of alcoholic poisoning, since we discovered that we had miscalculated the lethal dose. All the other dogs survived and showed no clinical or laboratory evidence of pathologic change other than temporary vasodepression following the intravenous injection of the extracts. In the light of the experiments to be described later it may be assumed that these experiments failed because the extracts were not sufficiently concentrated.

6. *Injection of the Same Extracts of Animals in Which Damage to the Liver Had Been Produced Previously by the Administration by Stomach Tube of a Combination of Carbon Tetrachloride, Cottonseed Oil and Alcohol.*—Carbon tetrachloride is a substance which has been proved, experimentally and clinically, to cause various degrees of necrosis of the liver. A few animals died promptly, and those which survived were given intraperitoneal injections of the extracts just described. In a few cases albumin, casts and red blood cells appeared in the urine, accompanied by an insignificant rise in the amount of nonprotein nitrogen, but in no case was the damage terminal or permanent. The conclusion is either that we did not damage the liver sufficiently to bring about the first stage of the hepatorenal syndrome or that we allowed so long a time to elapse between the production of the hepatic damage and the injection of the liver extract that full regeneration of the damaged liver cells had occurred. The inadequate concentration of the extracts is another factor to be considered.

7. *Intraperitoneal Injection of the Extract of the Liver of a Patient Who Died with Hyperpyrexia Thirty-Two Hours After Operation on the Biliary Tract.*—The patient, a woman, aged 57, submitted to

cholecystectomy for cholelithiasis and died promptly after operation with the typical syndrome of hyperpyrexia of Heyd's group 1 and our own group 1 A. At autopsy peritonitis was ruled out, as were hemorrhage, leakage of bile, embolism and pneumonia. A stone, undetected at operation, was found in the common bile duct, but it clearly played no part in the fatal outcome.

The liver was ground and extracted with physiologic solution of sodium chloride, with sterile distilled water and with alcohol, and each extract was injected into a separate dog intraperitoneally, the dosage being doubled each succeeding day. All the dogs died within seventy-two hours of the first injection, and all exhibited casts, albumin and red blood cells in the urine. This experiment was one of the first to be performed, and since its full significance was not then realized no determinations of the blood chemistry were made, which is, of course, a serious defect in our chain of evidence.

Autopsy on the dog given injections of the alcohol extract showed no significant changes, but in the dogs given injections of the saline and the watery extract there was marked parenchymatous degeneration of the liver cells, with similar degenerative changes in the convoluted tubules of the kidneys, as well as marked engorgement of the renal blood vessels and interstitial hemorrhage. Since this is precisely the histologic picture exhibited by the patients who died with the so-called hepatorenal syndrome, there seems no question that there was present in the extract made from the liver of the patient who died a "liver death" after operation on the biliary tract some substance capable of reproducing the histologic picture in experimental animals. There also seems no doubt, since only the saline and the watery extract reproduced it, that the substance, whatever its nature may prove to be, is water-soluble. We feel certain, as we have said, that we could have reproduced the same picture with the extracts made from the livers of the dogs which died after release of their experimental biliary obstruction had we made them in sufficient concentration.

8. *Implantation of Normal Liver into the Peritoneal Cavity.*—This experiment was previously carried out by Mason, Dragstedt, and Andrews and Hrdina.<sup>19</sup> We have repeated it in order that we might prove to our own satisfaction that the introduction of normal liver into the peritoneal cavity, while it causes the autolytic peritonitis described by the aforementioned authors, presents no parallel to the type of "liver death" in which damaged liver is the source of the lethal substance elaborated. We were able to duplicate their findings in all regards. We made careful studies of the temperature of these animals, hoping that we might obtain in this fashion some clue to the hyperpyrexia of Heyd's and of our own group 1, for which, as yet, we had

no explanation, but in no case was hyperpyrexia noted and in only 1 instance did the rectal temperature reach 105 F.

9. *Intraperitoneal Injection of Normal Liver*.—This experiment was also carried out by Mason, Dragstedt and Andrews and Hrdina. All of their dogs died within from seven to eighteen hours, with autolytic peritonitis. We were not able to duplicate these results, although we carefully reproduced the conditions of their experiments and used incubated, concentrated extracts of normal liver made up according to their directions. All the dogs which we used for this experiment lived and showed no reaction of any sort, temporary or permanent, other than a slight immediate reaction after the injection, which is to be expected. For our own purposes this series of experiments proved again that normal liver and diseased liver do not cause the same pathologic processes, but why we failed to reproduce the lethal results of the other experimenters we are at a loss to comprehend.

10. *Intravenous Injection of the Extracts of Normal Liver*.—These injections produced no clinical or laboratory results of any sort and need no detailed discussion.

To summarize, then, the results of these various experiments, we may say that traumatic necrosis of the liver to a sublethal degree, interference with the hepatic and the portal blood supply to the same degree and obstruction of the biliary tree failed to produce in experimental animals the hepatorenal syndrome seen in human patients after operation on the biliary tract. The experimental production of autolytic peritonitis, as well as the intraperitoneal and the intravenous injection of the extracts of normal liver, proved irrelevant to our purpose. On the other hand, the release of experimentally produced obstruction promptly initiated a clinical course and a postmortem picture, gross and histologic, precisely similar to the clinical and postmortem picture observed in human subjects who die under the same conditions after operation on the biliary tract. Injection of various extracts made from the livers of these animals failed to reproduce the same picture in other animals, chiefly, we feel now, because of errors in concentration of the extract. However, the same picture was reproduced by the injection of the saline and the watery extract of the liver of a human patient who died suddenly after cholecystectomy, with hyperpyrexia.

#### COMMENT

The conclusions to be drawn from this clinical and experimental study seem to us to be very clear and may be summarized as follows:

There is in all cases of biliary tract disease an associated hepatic state. Whether it is antecedent or consequent is still a matter of dispute and makes no special difference in this discussion. It can, however,

in certain cases be of enormous significance. If it is unaltered by the onward march of the disease, a hypothesis which is scarcely tenable, or if it is unaltered by operation, it will have no fatal consequences. The moment, however, it is altered by surgical release of the obstruction, however slight and trivial the obstruction may have seemed, it becomes progressively more severe, which brings one sharply up against the fact that the very means adopted to relieve the disease may kill the host, a situation analogous to operation for intestinal obstruction, for instance, in which the release of the obstruction often permits a fatal onrush of toxic intestinal contents into the still undamaged area of the bowel. This state of affairs is over and above all the other concomitants of operation, the risk of anesthesia, surgical trauma, changes of temperature and the anatomic changes consequent on the removal of the gallbladder from the bed of the liver.

One or two of these considerations must be mentioned in more detail. The effect of the anesthetic, for instance, quite aside from anything else, depends on the agent employed and on the amount of hepatic damage already present. The work of Rosenthal, Bourne and others, chiefly with dye tests, has shown that ether causes a definite although transitory impairment of hepatic function, rarely lasting longer than twenty-four hours, while Columbal and Ascoli, Kehr, von Haberer and Stahler, Wilensky and Colp and others have pointed out that in biliary disease, particularly when there is associated jaundice, hepatic and renal damage already exists which cannot fail to be intensified by the trauma of the anesthetic. On the other hand, cogent as these arguments are, they do not hold in all cases, for a large proportion of the "liver deaths" reported followed operations performed under other than ether narcosis.

Surgical trauma needs little discussion, for it is clear that the unavoidable trauma of a skilled surgeon will be many times increased by the inexperienced manipulations of a less skilled one. From the anatomic standpoint, Heyd<sup>21</sup> pointed out that, quite aside from the change in hydrostatics, the effect of any cholecystectomy is to leave in the liver a denuded fossa of varying extent, which is capable of transudation and absorption of protein. Furthermore, even in cases in which there is no obstruction the mere drainage of the gallbladder, let alone its removal, brings about, through changes in pressure, a reactionary hyperemia, and the operation of the ordinary laws of physics makes this reaction even more acute and more extensive in cases of obstruction.

Another point which cannot be ignored is that even the slight exposure attendant on merely opening the abdomen reduces the tem-

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21. Heyd, C. G.: "Liver Deaths" in *Surgery of Gallbladder*. J. A. M. A. **97**: 1847 (Dec. 19) 1931.

perature of the liver, as Crile has shown, from 1.5 to 3 degrees. This same investigator has also shown that there is a decrease in the chemical activity of this organ by some 10 per cent for every drop in temperature of 1 degree and that if disease has reduced its activity by as much as 10 per cent a reduction of temperature by even 1 degree is likely to result fatally.

We need scarcely discuss the point that if these things are true of the normal liver they are even more likely to be true of the sub-normal or abnormal liver. Furthermore, no absolutely satisfactory test as yet exists by which the surgeon can measure the degree of hepatic function. The most accurate test available still gives only approximate results. The amount of damage to the liver, as we know, bears no special relation to the amount of pathologic change in the biliary tract, indeed, it may be entirely inverse to it. In advanced cases of disease of the biliary tract the surgeon suspects a high degree of hepatic damage, even if he cannot estimate it exactly, but in the type of cases we are investigating, in most of which there is an absolutely or a relatively good risk, he has little help from the laboratory. In other words, the surgeon knows, as a matter of general knowledge, that some degree of hepatic damage is always associated with any degree of damage to the biliary tract, but whether it is extreme or minimal he has no accurate way of determining.

So far, then, the chain of events is this: The patient with or without gross obstruction of the biliary tree has some degree of hepatic damage, but it is not incompatible with life. So long as the liver is put to no strain and stress other than that of ordinary living, to which it has accustomed itself, so to speak, it is quite capable of carrying on. But when operation is undertaken, an entirely different complexion is put on the matter. Even in the most favorable cases there are introduced, alone or in combination, the factors we have just been discussing, the strain of the anesthetic, the trauma of surgical manipulation, the drop in intra-abdominal temperature and the changes in intra-hepatic and biliary pressure. The result is that a liver which is already the seat of a pathologic process is unable to cope with the added strain, and its function promptly fails. It is already the seat of a permanent and more or less marked toxic reaction, and it cannot fulfil the further demands on its economy as could a normal organ. The toxic substances which reach it in the course of normal body metabolism are thrown off undetoxified, and the liver cells, as they become increasingly unable to fulfil their function, undergo some necrotic change, partly because of failing function and partly because of the changes in intrahepatic pressure brought about by operation. The circulation, therefore, is filled both with the undetoxified substances which the liver has been unable



to handle and with, we postulate, some toxic substance cast off by its own necrosed cells.

The next assumption is an entirely logical one. The kidney is, after the liver, the great detoxifying organ of the body, and once the liver has failed in function, the kidney, purely as a matter of physiology, must take up its work. But the difference is that while the margin of safety in the liver is enormous, the margin of safety in the kidney is slight. The kidney is not fitted by nature, as is the liver, to detoxify, either quantitatively or qualitatively, the normal products of body metabolism, let alone, in addition, the toxic substances elaborated by the damaged liver cells. The result is that it promptly breaks down, and an overwhelming toxemia is the natural consequence.

The physiology of the kidneys is too well established to need repetition here, but one point should be emphasized, i. e., that toxic products are excreted through the convoluted tubules. This has been established experimentally by the use of salts foreign to the blood, and the same process would be operative with the toxic products of necrosed liver cells. The pathologic result, so to speak, is just what one would expect in the light of those facts. The sensitive epithelium of the convoluted tubules shows changes ranging all the way from slight granular changes to complete necrosis and sequestration, while the glomeruli remain practically undamaged. The clinical phenomenon is, as we have noted, oliguria which progresses to anuria, in spite of the undiminished if not actually increased fluid intake always forced on the patient in an endeavor to correct his perverted blood chemistry.

Our personal opinion, which we think is substantiated by the clinical and experimental facts we have stated, is that the hepatic damage always precedes the renal damage and that if the patient who dies promptly with hyperpyrexia and shows hepatic changes at postmortem examination could be kept alive long enough he too would show precisely the same clinical and postmortem renal changes as does the patient who dies later. The patient who dies promptly undoubtedly has a more overwhelming toxemia, perhaps qualitative but more probably quantitative, than the patient who dies after cardiorespiratory collapse (group 2 B), while death which occurs after from ten to twenty days is best explained in the light of our present knowledge as due to protein intoxication in contrast to the probable anaphylactic reaction of early death with high temperature. The patient has a preexisting hepatic damage; small amounts of the toxic substance elaborated in the damaged liver cells are released into his system, but he is sensitive to the substance and can handle it. He cannot, however, handle the massive amounts released postoperatively. Furthermore, even though his damaged liver can stand the strain and stress of ordinary life, it cannot withstand the

added strain and stress of surgical trauma and its concomitants, and his kidneys, especially if they are in any way prediseased, as they so often are in persons of advancing years, have no margin of reserve.

We make no claim for originality for this theory, except in certain details, but we do claim that we have established it in some regards by experimental proof which has not hitherto been adduced, and we have carried it, we believe, slightly further than have the other investigators who have supported it. A brief review of the various other theories which have been advanced to explain the problem of "liver deaths" might be profitable at this point:

Heyd, the first to consider "liver death" as a distinct postoperative entity in disease of the biliary tract, expressed the belief that in the group 1 type of death (with rapidly increasing hyperpyrexia) certain deleterious substances are released at operation, the whole mechanism suggesting complete and rapid cessation of hepatic function, and that in the second group (death with hyperpyrexia within from forty-eight to seventy-two hours), there is a toxic inundation of the system and direct poisoning of the liver cells, again with cessation of hepatic function. In the third group (deferred death with renal symptoms), according to him, death is due to throwing on an already damaged liver the burden of detoxifying an increment of deleterious products released by operation, the result being a progressive increase of hepatic dysfunction.

Heyd also advanced the theory, which is purely speculative, as he himself admitted, that in the group of cases in which pancreatic disease is a factor the underlying cause of death may be some pancreatic toxemia. Aside from the fact that the existence of a pancreatic toxin has never been demonstrated, this theory in no way explains the cases in his own group 1 and group 2, in which pancreatitis plays no part. His theory of hepatic dysfunction is, of course, the same in its essence as the majority of the theories since advanced to explain these deaths; it does not, however, go far enough to include the renal aspect, nor does it explain the details of the mechanism.

Cave's idea is much the same, i. e., that the sudden liberation of toxins from the liver or of pieces of chemically altered liver cells into the general circulation is responsible for the catastrophe. He mentioned as other possible causes the stirring up of infected bile in the intrahepatic ducts as the result of operative manipulation and the partial cessation of hepatic function caused by the shock of the actual removal of the external biliary viscus from its bed, with the resulting exposure of the surface of the liver. The latter considerations, of course, are operative in fatal and nonfatal cases alike, and the toxic theory, while it is correct in its fundamental conception, does not go far enough.

Ravdin and Behrend suggested that the syndrome may be due to the accidental ligation of the hepatic artery, which is anomalously placed in a high percentage of cases, as high, according to some authorities, as 33 per cent. Even granting that any interference with its blood supply is naturally likely to affect the liver in some way, this theory does not explain those cases in which anomalies of the vascular supply are absent, as has been proved by autopsy in many reported cases, while our own experiments and those of Helwig and Schutz seem definitely to disprove it. Such a theory, furthermore, does not explain the cases of traumatic necrosis of the liver and kidney reported by Furtwaengler, Helwig and Orr and ourselves, in which the same syndrome is present but in which an anomalous blood supply could play no possible part.

Guthrie and Robertson<sup>22</sup> suggested that the administration of ether may be the cause of the "liver deaths" and pointed out that in their own clinic, in which ether is never used in abdominal operations, no fatality in 434 operations on the biliary tract seems to fall into Heyd's group 1. The first objection to that theory is that in many reported cases ether anesthesia was not used. The second is that in our own opinion at least 1 case which they report in detail in their series of early deaths after operation on the biliary tract and which they themselves set down as due to hepatic failure and classify as Heyd's group 3, seems to us to fall into group 1: A woman, 24 years old, died suddenly, with high temperature, thirty-three hours after cholecystectomy and exploration of the common bile duct; there was pronounced cardiorespiratory collapse immediately before death. Two other cases described by the same authors seem to us, in the absence of complete details, to be possible examples of deferred deaths with uremic symptoms, while they themselves classify 2 other cases, described in detail, as probable examples of Heyd's group 3. Postmortem observations are not given in any of these cases, and discussion of them, therefore, is little more than speculative.

Stanton mentioned Crile's suggestion of a relationship between the thyroid, the adrenals and the liver as worthy of consideration, and he mentioned also the suggestions of various surgeons with whom he discussed the condition, which include injury to the nervous mechanism of the liver and the absorption of toxic bile or of diseased or chemically altered liver cells. Connell expressed the belief that the mechanism of death is some chemical or metabolic reaction of an unknown nature.

Walters and Parham emphasized the difference between hepatic and renal insufficiency in these cases in a report published in 1922,

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22. Guthrie, D., and Robertson, H.: Is Ether a Cause of "Liver Death" Following Gallbladder Surgery? *Guthrie Clin. Bull.* 2:11 (July) 1932.

before the full significance of the syndrome was realized, but in the light of more recent work, and particularly in the light of our own experimental studies, we cannot accept this distinction. Willard Barlett Jr., seemingly inclined to emphasize the same distinction, stated that there is no evidence that hepatic cell damage serious enough to cause renal damage must precede the pathologic process in the kidneys, his idea being that infection of the bile passage and not some toxic phenomenon is the cause of the nephritis. We are speaking, as we have already pointed out, of cases which for the most part are not parallel, but we cannot agree with his theory even for the comparable cases for several reasons. In the first place, we do not think that it is logical to disregard the hepatic factor which is apparent to some degree in all cases of biliary tract disease. In the second place, all cases in which the hepatorenal syndrome is present are not associated with infection of the bile passages. Stanton, who was at first inclined to the theory of infection, discarded it for just that reason, especially after he had encountered the case of traumatic necrosis of the liver in which the same syndrome was noted but in which infection could not possibly have played any part. Finally, if infection of the bile passages were the cause of this syndrome, the nephritic factor would be apparent in more cases after operation, instead of which its incidence, in proportion to that of infection, is really quite small.

Ransahoff, noting the shocklike states which sometimes supervene immediately after operations on the common bile duct, advanced the theory that the cause is a sudden stretching or pulling forward of the structures in the gastrohepatic omentum, with consequent constriction of the portal vein, but this, as Ravdin pointed out, is not an adequate explanation; it does not explain cases of deferred death, nor does it explain those cases in which the common bile duct is not handled. Ravdin himself advanced the vasodepressor theory, which, it must be admitted, has much to be said for it. Vincent and Sheen, he pointed out, as early as 1903 were able to extract from the liver a depressor substance, and he himself, working along this line, was able, after experimental ligation of the common bile duct, to obtain a substance containing histamine and choline, both of which are notoriously vasodepressant in action. His theory is that an overwhelming amount of this substance is suddenly released at operation or, as Helwig and Orr pointed out, after trauma of the liver. Theoretically, the latter authors added, such a substance might cause sufficient vasodilatation to produce renal damage, but Ravdin himself, so far as we can gather, does not draw that conclusion. Again, it has been proved that the amount of depressor substances in jaundiced hepatic tissue is considerably in excess of the amount in unjaundiced tissue, so the

explanation, it seems to us, is not particularly helpful for those cases which really furnish our chief problem, those in which the disease of the biliary tract is not of extreme degree. We have no doubt that Ravdin's theory is correct, but we do not believe, nor, for that matter, does Ravdin himself claim, that vasodepression is the chief cause or the only cause of the hepatorenal syndrome.

Wilensky advanced the idea that the initial lesion in the biliary tract produces a primary effect on the hepatic cells and a secondary effect on the renal apparatus, it being highly probable that in hepatic disease some of the catabolic products of liver metabolism and the end-products dependent on its injury are not without effect on the kidney. Such an explanation covers the picture of uremia associated with the so-called cholemia or hepatic toxemia, but it does not provide, as does our theory, for the successive steps of the injury extending from the biliary tract into the liver cells and thence into the convoluted tubules of the kidneys. Basically it is correct, but again details are lacking.

Furtwaengler believed that his patient, in whom bilateral necrosis of the cortices of the kidneys followed traumatic necrosis of the liver, had a latent tendency to vascular spasm due to some nervous disposition, and that the necrosis of the renal cortices resulted from ischemia produced by some hypothetic chemical toxin circulating in the blood and rising from hepatic decomposition. We see no particular necessity for introducing the idea of a tendency to vascular spasm; indeed, we think it highly improbable that it could be a common factor in all cases of trauma, let alone in the similar cases following operation on the biliary tract, which we, together with Stanton and with Helwig and Orr, believe to belong in the same pathologic group. Helwig and Orr properly discard the theory that jaundice is responsible. Undoubtedly it can cause a certain degree of renal damage, but, as they pointed out, in their case the picture was not one of true biliary nephrosis, while jaundice was no part of the picture in Furtwaengler's case, and it was noted in only 1 of the 6 cases of trauma to the liver which we ourselves are reporting.

The explanation for the hepatorenal syndrome advanced by Helwig and his co-workers, Schutz, Kuhn and Orr, is that some potent poison is elaborated in the necrotic hepatic tissue which has a specific effect on the renal parenchyma, causing progressive degeneration and sometimes complete necrosis of the tubular epithelium. They believe that the specific action on the kidney is proved by the fact that other highly specialized viscera, which invariably show the same type of parenchymatous degeneration in the presence of circulating toxins, do not show it in this condition. With the premise of this theory, that some toxic substance is elaborated by the damaged liver cells, we are in complete

agreement. We do not believe, however, that it is necessary or even logical to postulate a specific action on the kidney. The kidney is the normal organ of excretion. Foreign proteins are excreted through its convoluted tubules, and in the so-called hepatorenal syndrome parenchymatous degeneration occurs in the tubules and nowhere else. It is unnecessary, in our opinion, to seek for a more complicated explanation. The kidney, we believe, suffers not through any specific action of the toxic substance released by the liver cells but simply in the fulfilment of its normal physiologic function, or, to speak more accurately, in the fulfilment of the abnormal duty suddenly placed on it. The possible effect of the toxin on the kidney tissue must also be taken into account.

We have already intimated that with the passage of time it has been suggested by various writers on the subject that this particular syndrome, either prompt or somewhat deferred death with hyperpyrexia, or deferred death with uremic symptoms, is not limited to operation on the biliary tract. Heyd, who first described this syndrome, classified in a special group the cases in which there was no biliary tract disease but usually pancreatic disease or more rarely gastro-intestinal disease and in which the same postoperative syndrome was apparent. We have already substantiated his cases of pancreatic involvement with 4 cases from our own records. The traumatic cases reported by Furtwaengler, Stanton and Helwig and Orr we have been able to parallel with a group of 6 cases following gunshot wounds or traumatic injuries of the liver. Wilensky is of the opinion that the same syndrome may be apparent in cases of burns, drug poisoning and high intestinal obstruction. The case of apiol (parsley camphor) poisoning reported by Thiers which terminated in death with the hepatorenal syndrome seems an instance of this sort. Helwig and Schutz reported in their group of 6 cases 1 in which the uremic syndrome was apparent eleven weeks after an operation for carcinoma of the breast, and they mentioned a case reported by LeNoir in which an operation for gastric ulcer terminated in death, with the hepatorenal syndrome.

Heuer, who denied any personal experience after operation on the biliary tract with cases falling into Heyd's and our own group 1, mentioned a case in which splenectomy was performed for supposed Banti's disease, in which later the condition proved to be either reticulosarcoma or Hodgkin's disease and in which death with hyperpyrexia occurred within twenty-four hours. We recently encountered a somewhat similar case in our own service. The patient, a Negress, who was regarded as presenting an excellent surgical risk, was submitted to resection of the cecum for chronic typhlitis. She died within seventy-two hours with an axillary temperature of 105.2 F. and a nonprotein nitrogen content of 76 mg., in contrast to a preoperative level of 29 mg. Autopsy

eliminated the possibility of peritonitis and other surgical complications and revealed the hepatorenal changes typical of the syndrome we are discussing. In another case of carcinoma of the pancreas with metastasis to the liver the same changes were noted.

Connell, writing in 1931, stated that the syndrome of sudden death with hyperpyrexia, was not apparent after any operation other than that on the biliary tract, but he withdrew the observation, as we have stated, in his last paper on the subject, and mentioned its occurrence following operations for ovarian cyst, uterine fibroid tumors, chronic appendicitis, ventral hernia and fracture of the skull. It is true that in at least one of those patients there was a former operation for biliary tract disease, and it is also true that cranial injuries are notoriously prone to produce high temperature reactions, but the list of cases, even with those exceptions, is impressive. Furthermore, in the 26 cases of postoperative heat stroke reports of which were collected by Cutting, only a few, as Connell pointed out, followed operation on the biliary tract, and there is little doubt that most of them, in view of the present knowledge would fall into the category we are discussing.

In the light of these suggestions we studied the results of a series of autopsies, casually selected and all of recent date, performed in cases of burns, intestinal obstruction and disease of the thyroid, and we were struck with the parallelism, which we noted again and again, between those cases and the cases in which death followed hyperpyrexia and the hepatorenal symptoms after operation on the biliary tract. In most instances, too, when the clinical course was typical, the postmortem changes were also typical, necrotic changes in the liver, with or without similar changes in the convoluted tubules of the kidneys, depending on how long the patient lived after operation or injury. We have no doubt that similar sudden deaths, with high temperature, occurring in cases of appendicitis and of kindred conditions might well be included, but we have not chosen to consider them because the element of infection naturally distorts and confuses the picture.

We are particularly impressed with the occurrence of the hepatorenal syndrome in cases of disease of the thyroid. The hepatic factor, of course, is no new thing, but we are not aware that the renal aspect has heretofore been particularly emphasized. Weller,<sup>23</sup> for instance, in 44 autopsies in cases of hyperthyroidism, found evidence of marked hepatitis in 22 and moderate hepatitis in 16, while in only 6 cases in the series was the liver normal. In a control series of other conditions he noted precisely reverse conditions, i. e., 30 cases in which there was no evidence of hepatic involvement, 13 with slight involvement and only

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23. Weller, C. V.: Hepatic Lesions Associated with Exophthalmic Goiter, *Tr. A. Am. Physicians* 45:71, 1931.

1 case with marked involvement. Rowe,<sup>24</sup> studying nearly 4,000 cases of various diseases, found the incidence of hepatic involvement, even including figures which he describes as "heavily over-weighted," to be at most 10.91 per cent, whereas in 644 cases of hyperthyroidism the incidence of hepatic disease was 22.44 per cent, nearly twice as great. Kerr and Rusk,<sup>25</sup> in 1922, reported a case of hyperthyroidism in which autopsy revealed what amounted to acute yellow atrophy of the liver, with marked parenchymatous changes in both the liver and the kidneys, and in a paper written in 1930 Kerr<sup>26</sup> mentioned several somewhat similar cases observed since then.

The most indubitable proof, however, has been advanced experimentally by Hashimoto,<sup>27</sup> in 1921, his experiments being confirmed by Goodpasture in the following year. They fed albino rats with thyroid substance in an endeavor to reproduce the myocardial changes of disease of the thyroid observed in human patients, and they reproduced not only those changes but also parenchymatous changes in the liver and in the convoluted tubules of the kidneys.

One wonders, in the face of this evidence, whether this syndrome is not considerably more frequent than is realized. Crisp,<sup>28</sup> for instance, reported from the Mayo Clinic a case of "secondary shock" which occurred twelve hours after resection of the rectum for a malignant condition, too early for peritonitis and too late for surgical or anesthetic shock. The temperature rose to 105.4 F., and there were all the classic signs of extreme toxicity; renal function, however, was unimpaired, and recovery followed. Keith, discussing this case, mentioned three personal cases in which exactly the same syndrome developed, with a fatal termination each time. The liver is not described, but autopsy showed cloudy swelling of the kidneys. Keith introduced the idea that perhaps the syndrome is due to the products of anaerobic bacteria, but one wonders whether his cases, as well as Crisp's case, might not be still other instances of the hepatorenal syndrome.

#### CONCLUSIONS

Our experimental study has not yet progressed to the point at which we feel that we can make suggestions of any value to prevent

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24. Rowe, A. W.: Endocrine Studies: XXXV. Association of Hepatic Dysfunction with Thyroid Failure, *Endocrinology* **17**:1 (Jan.-Feb.) 1933.

25. Kerr, W. J., and Rusk, G. Y.: Acute Yellow Atrophy Associated with Hyperthyroidism, *M. Clin. North America* **6**:445 (Sept.) 1922.

26. Kerr, W. J.: Necrosis of Heart and Liver in Thyrotoxicosis, with Some Notes on Possible Changes in Other Organs, *Northwest Med.* **29**:430 (Sept.) 1930.

27. Hashimoto, H.: Heart in Experimental Hyperthyroidism with Special Reference to Its Histology, *Endocrinology* **5**:579 (Sept.) 1921.

28. Crisp, N. W.: Toxemia Producing Shock After Operation, *Proc. Staff Meet., Mayo Clin.* **5**:128 (May 7) 1930.



the distressing catastrophe of "liver death." The most important consideration, it seems to us, lies in Graham's rather casually uttered statement that there is little doubt that the patient with a damaged liver presents a questionable risk not only for operations on the biliary tract but for any operation, no matter how trivial it may be. Other writers, notably Shearer<sup>29</sup> within the last year, have made the same point, and that warning, taken at its face value, will mean, for all practical purposes, a surgical revolution. It will mean that there will be no more "simple surgery." It will mean, particularly, that the surgeon who proposes to perform operations on the biliary tract not only must remember that hepatic disease of some degree is an invariable concomitant of biliary tract disease of any degree but must regard all his candidates for such operations as presenting potentially poor risks, regardless of how incongruous their inclusion in such a category may seem. It means, to go further, that all candidates for any operation must be studied from the standpoint of hepatic function and that the ninety and nine must be discommoded and inconvenienced to rescue the one who may otherwise be lost.

At present, however, no test is available which gives anything but an approximate idea of the efficiency of hepatic function. The details of such tests are no part of this paper, but it seems nothing but fair to call attention to the results achieved by Graham,<sup>30</sup> the best on record, we would say, and certainly worthy of emulation. Using iso-iodoikon and taking a 50 per cent retention as an arbitrary standard of safety for operation without elaborate preparation, he was able to reduce his mortality in simple cholecystectomy from 6 per cent in 216 cases to 0.4 per cent in 224 cases, while in operations on the common bile duct his mortality fell from 7.7 to 2 per cent. Regardless of how inaccurate a test may be, it is worthy of routine use if it can produce results such as those.

In the same connection we consider Wilensky's suggestion of real value, that hepatic function be estimated in the light of renal function and that evidence of renal insufficiency in cholelithiasis and kindred diseases be regarded as presumptive evidence of hepatic insufficiency.

Preoperative preparation, as Shearer in particular pointed out, seems as wise for the patient who apparently presents a good risk as for the patient who frankly presents a poor risk. It should include, according to the indications, a diet high in carbohydrates, fluids by all routes, dextrose as necessary, orally and intravenously, and calcium.

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29. Shearer, J. P.: Mortality Following Gallbladder Surgery, *Ann. Surg.* **98**: 1114 (Dec.) 1933.

30. Graham, E. A.: Estimating Risk of Operations on Biliary Tract by Testing Excretory Function of Liver, *Radiology* **21**:191 (Aug.) 1933.

not so much for the control of possible hemorrhage as because Lamson, Minot and Robbins have shown (Graham) that hepatic damage caused by carbon tetrachloride is repaired more rapidly under this form of therapy.

It seems scarcely necessary to say that the anesthetic should be chosen with judgement and that ether should positively be avoided in the presence of actual or presumptive hepatic damage. Manipulations should be conducted with as little trauma as possible. Unnecessary and prolonged exposure of viscera should be regarded as definitely harmful. The suggestion of Crile that diathermy be used in abdominal operations to maintain body temperature has not been generally adopted, but occasional reports, most recently from the clinic of Sobre-Casas in Buenos Aires, testify to its worth (Eiss<sup>31</sup>).

Gradual decompression of the obstructed biliary tree, in the light of clinical evidence and of our own experimental evidence that it is not the obstruction but the release of the obstruction which does the damage, seems worthy of adoption. Culligan recently described a method which involves drainage of small quantities of bile, from 6 to 10 cc., at intervals of thirty minutes for the first four days after operation, at the end of which time it is assumed that the liver has been able to readjust itself gradually to the new pressure so that no sudden enlargement of the capillaries of the portal system can occur. He gave no statistics but stated that since he adopted this plan he had no case of either postoperative hemorrhage or so-called hepatic insufficiency. The method implies personal nursing, which would make its routine use difficult in public institutions or, for that matter, in many private ones without special nursing, but it is clearly a wise precaution.

Mann, as Helwig and Schutz mentioned, suggested that it may actually prove inadvisable to suture the liver after cholecystectomy, for fear of bringing about sufficient necrosis of liver cells to release toxic products into the circulation in the light of his own demonstration that the most profound acute and chronic changes are found in the hepatic parenchyma in the region of the gallbladder, this seems a perfectly logical idea. More than one writer has suggested, too, that the patient's interests may be better served by cholecystostomy than by cholecystectomy, and while the practice may be open to objection on many counts, it does not seem, as Walton Martin<sup>32</sup> pointed out in 1927, to predispose to hepatitis. In a valuable discussion of the relation between hepatitis and cholecystitis he made the point that in the era when

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31. Eiss, S.: Conservation of Hepatic Function in Gallbladder Operations, *Ann. Surg.* **98**:348 (Sept.) 1933.

32. Martin, W.: Hepatitis and Its Relation to Cholecystitis, *Ann. Surg.* **85**: 535 (April) 1927.

cholecystostomy was the common practice no report was ever made in which the retention of even a grossly infected, drained gallbladder set up chronic hepatitis.

Finally, a point made by many writers is undoubtedly worthy of earnest consideration, that since these catastrophes, whatever may be their immediate cause, invariably have for their ultimate cause delay in the institution of surgical measures, there seems to be no logic or reason for the prolonged medical treatment of cholecytic disease. That advice is not to be taken, of course, as warrant for the performance of cholecystectomy on insufficient indications, particularly on the indication of so-called biliary dyspepsia, or for the performance of operations for the acute disease unless one's convictions happen to take that trend, as the convictions of many still do not. It does seem reasonable, however, not to permit a pathologic process to continue without restraint when its end-results can be as serious as the experiences of every surgeon have proved these to be.

We feel that by this experimental and clinical study we have clearly proved the definite cause and effect relationship between disease of the kidneys and disease of the liver associated with or consequent on disease of the biliary tract, the so-called hepatorenal syndrome. We feel that we have proved that this syndrome occurs not as the result of obstruction but as the result of the release of the obstruction. And we feel that we have proved that the underlying cause of the process is some toxic substance which is water-soluble, which is released by the necrosed cells of the liver and the action of which on the kidneys is not specific but simply a corollary to an overtaxed normal physiologic process, the excretion of foreign proteins by the convoluted tubules. We have evolved the theory, partly from the studies of others and partly from our own clinical and experimental studies, that the so-called hepatorenal syndrome is a pathologic process which may be most marked and most dramatic after operation on the biliary tract but which may occur in several, perhaps many, other diseased states. This theory is that the damaged cells of the liver fail in their function and release thereby some potent toxic substance, which, circulating in the blood, is excreted by the kidneys, but which is so potent that the convoluted tubules, unfitted by nature for such a load, break under it. We believe, further, that in cases in which sudden death occurs with hyperpyrexia, that the hepatic changes, which are the only changes apparent at autopsy, are simply the first stage of the same process which in some cases later terminates in deferred death, with renal as well as hepatic damage.

This report is, as we have mentioned, entirely preliminary. There is still much to be explained. We have as yet no explanation for the hyperpyrexia in the group 1 cases other than the rather vague theory

of an anaphylactic reaction. That the elevation of temperature is in some way related to the liver we are quite sure, our belief being substantiated by the experiments of Andrews, Petersen and Boikan,<sup>33</sup> which establish the fact that in the absence of the liver in eviscerated animals bacterial injections which would ordinarily produce high temperature reactions produce none at all. An endeavor to reproduce these elevations of temperature in animals will be our immediate concern.

We propose, too, to endeavor to isolate the hypothetic toxic substance we have described, and here we shall follow the suggestion of MacDonald and his co-workers<sup>34</sup> that the urine rather than the blood or the tissues is the most potent source of supply for foreign proteins. We shall endeavor to isolate it in such a form that it can be reinjected, with the idea of thus reproducing the hepatorenal lesions we are studying.

We plan, furthermore, to repeat our experiments following hepatic damage with carbon tetrachloride, with prompter injection of the extracts containing the hypothetic toxin. Finally, as clinical material becomes available, we shall repeat our experiments with extracts of the liver of patients dying with hepatic insufficiency, and we shall use these, as well as the extracts of the liver of experimental animals in which obstruction and release of the biliary tree has been done, in stronger concentration. We shall also make more complete observations on the blood chemistry than we have hitherto made.

#### SUMMARY

The previous literature of so-called "liver death" is briefly reviewed and its various aspects are correlated.

Twenty-three cases of various types of "liver death" following operation on the biliary tract are analyzed. To this number are added 4 cases following operation on the pancreas and 6 cases of traumatic injury to the liver, all of which present the same syndrome.

A series of experiments designed to reproduce the syndrome in experimental animals is reported, and those experiments which were successful are discussed in detail.

The theory is advanced that sudden death, with high temperature, and the so-called hepatorenal syndrome are successive stages of the same pathologic process. The presumptive mechanism of this process is set forth.

The theories of "liver death" hitherto advanced are analyzed.

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33. Andrews, E.; Petersen, W. F., and Boikan, W.: Observations of Eviscerated Dogs, *Proc. Soc. Exper. Biol. & Med.* **25**:109 (Nov.) 1927.

34. MacDonald, R. F.; Thomas, W. A., and Andrews, E.: Preparation of Blood-Free Tissue Proteins, *Proc. Soc. Exper. Biol. & Med.* **25**:246 (Jan.) 1928.

The occurrence of the same syndrome in other conditions, such as burns, intestinal obstruction and disease of the thyroid, is noted, and its relation to the latter diseases is discussed.

Further lines of investigation are outlined.

This work has been done with the cooperation and approval of Dr. Urban Maes, director of the Department of Surgery of the Louisiana State University Medical Center. We have been materially aided in the experimental phase of the study by Dr. Ralph Lambert of the Department of Surgery, Dr. Louis Lichtenstein of the Department of Pathology and Dr. W. B. Wright of the intern staff of the Charity Hospital. Miss Genevieve Montz, technician in the Department of Surgery, is responsible for all of the laboratory work.

## SEQUELAE OF PEPTIC ULCER FOLLOWING MEDICAL AND SURGICAL TREATMENT

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It has now become generally understood that the treatment of peptic ulcer consists of a thorough medical regimen before an operation is considered. For that reason physicians are now encountering complications from prolonged medical management as well as those which result from improper selection of patients that need to be operated on.

It seems better not to differentiate between gastric and duodenal lesions on the ground of malignant transformation. The etiology is apparently the same for both gastric and duodenal lesions, and the symptoms are essentially the same. Most clinicians that have had the opportunity to observe the clinical course of gastric neoplasm and of gastric ulcer under medical management feel definitely that malignant transformation in gastric ulcer is rare. For that reason one need not be concerned with a different method of treatment of gastric and of duodenal ulcer to prevent malignant changes. Certainly, experience in the clinic for gastric diseases of the Fourth Medical and Surgical Division of the Bellevue Hospital shows that the occurrence of malignant degeneration in gastric ulcer<sup>1</sup> is practically negligible. It is worth while to call attention to the fact that carcinoma of the duodenum<sup>2</sup> is not an uncommon observation but that at present there is no authentic case of malignant degeneration of duodenal ulcer. This helps to support the contention that carcinoma of the stomach is really a rare sequela of gastric ulcer. At the onset carcinoma may resemble an ulcer in gross appearance, but the symptomatology and clinical course are entirely different in carcinoma and in gastric ulcer.

The internist now dictates, in the majority of instances, the time at which a patient with ulcer is referred for operation. As a result a high percentage of patients are carried too long under medical treatment. Certain complications arise which could have been prevented if the

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Clinic held before the Graduate Fortnight of the New York Academy of Medicine on Oct. 22, 1934.

1. Hinton, J. W.: Clinical Consideration of Gastric Ulcer and Carcinoma. *Arch. Surg.* **27**:395 (Aug.) 1933.

2. Hinton, J. W.: Does Carcinoma of the Duodenum Ever Arise from Duodenal Ulcers? *Am. J. M. Sc.* **181**:843 (June) 1931.

patient had been referred for operation at an earlier date. One of these complications is chronic pancreatitis, and the second, massive hemorrhage of a recurring nature. These are two complications of ulcer occurring under medical treatment that necessitate surgical intervention. Chronic pancreatitis is really the one true indication for referring a patient suffering from chronic ulcer for operation. One encounters difficulty in making an early diagnosis of such an associated disease, as there are no laboratory aids that are of definite help at this time and one has to rely on the changing symptomatology and on clinical judgment.

The history is the most important aid in the diagnosis of chronic pancreatitis<sup>3</sup> in the advanced stages. The patient usually says that his pain is more severe than at the onset of his complaints and that the dull discomfort which he had when the ulcer was first diagnosed has disappeared. Food gives little relief; he is awake several hours at night because of pain, and he frequently requires sedatives before he can sleep. The pain radiates directly through the lumbar region and is usually felt on both the right and the left side of the spine. Physical examination reveals epigastric tenderness and tenderness over the lumbar region which is usually marked on both sides of the spine; the results of physical examination are otherwise normal. The usual laboratory tests help little in the prognosis<sup>4</sup> of the course of ulcer. My associates and I carried out the amylase test of the blood serum according to the method of Elman and his co-workers<sup>5</sup> and the lipase test of the serum according to the method of Cherry and Crandall,<sup>6</sup> in the hope of detecting cases of early chronic pancreatitis before the symptomatology of ulcer had changed; it was hoped that with infection and fibrosis of the pancreas the amounts of amylase and lipase would be constantly reduced in patients suffering from associated pancreatitis, but the results were extremely variable and of no clinical significance. After employing the tests on forty patients, we discontinued their use. While carrying out experiments on dogs in which we ligated the pancreatic ducts to produce changes in the thyroid gland, we studied the content of amylase and of lipase in the blood of fifteen of the

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3. Hinton, J. W.: Chronic Pancreatitis Associated with Peptic Ulcer, *Arch. Surg.* **28**:580 (March) 1934.

4. Hinton, J. W., and Frankel, Sophie: The Significance of Laboratory Studies in Gastric and Duodenal Ulcers, *Am. J. Surg.* **17**:25 (July) 1932.

5. Elman, Robert; Arneson, Norman, and Graham, E. A.: Value of Blood Amylase Estimations in the Diagnosis of Pancreatic Disease, *Arch. Surg.* **19**:943 (Dec.) 1929.

6. Cherry, I. S., and Crandall, L. A.: The Specificity of Pancreatic Lipase: Its Appearance in the Blood After Pancreatic Injury, *Am. J. Physiol.* **100**:226 (April) 1932.

animals at weekly intervals until they died. The average duration of life was four weeks. Even in the animals in which complete fibrosis of the pancreas developed, the results of the tests were variable and could not be considered of clinical significance.

#### REPORT OF CASES

Two cases are reported to illustrate the importance of the history in making a diagnosis in these cases.

CASE 1.—A woman, aged 52 years, was seen first on Jan. 17, 1934, complaining of abdominal pain of two and a half years' duration.

The patient stated that in July 1931 she had had a sudden attack of severe pain in the upper part of the abdomen, which necessitated her calling a physician. He gave her an injection of morphine, and the pain was immediately relieved. The next day she felt well. She was then told that her gallbladder was diseased. A few days later roentgenograms were taken of the stomach and gallbladder, which revealed disease of the gallbladder and a normal stomach. The patient then was careful of her diet and had no complaints until three months before consulting me, when she began to have slight discomfort in the upper part of the abdomen but no severe pain. Ten days before her visit to my office she had another attack of severe pain in the upper part of the abdomen, which necessitated her physician's giving her an injection of morphine. She was in bed four days with slight fever, attended by a nurse. Her physician told her that she had a diseased gallbladder and advised operation.

Examination revealed slight epigastric tenderness, but no masses were felt in the abdomen. Moderate tenderness was detected under the right costal arch. The results of urinalysis were negative; the blood count revealed 4,400,000 red cells, 96 per cent hemoglobin (Sahli), 4,100 white cells and 64 per cent polymorphonuclears. Roentgenography failed to visualize the gallbladder after the administration of a dye.

A diagnosis of cholecystitis and cholelithiasis was made, and the patient was operated on at the New York Post-Graduate Medical School and Hospital on Jan. 20, 1934.

*Operation.*—When the abdomen was opened a normal gallbladder was observed, both on inspection and on palpation. Both kidneys were seen to be normal in size and position. The stomach appeared normal, but on palpation of the common duct it was observed that the pancreas was enlarged and contained a mass as large as an average-sized orange and that the duodenum was adherent to the mass. The diagnosis of perforated ulcer of the posterior portion of the duodenum was made, and a resection of the stomach was then performed, with removal of 75 per cent of the stomach and of 1½ inches (3.81 cm.) of the duodenum. An ulcer the size of a 25 cent piece, which had perforated into the pancreas, was observed in the posterior portion of the duodenum. A pancreatic abscess exuded pus at the time of operation. An anticolie anastomosis was made without entero-enterostomy, and the abdomen was closed in anatomic layers with drainage. The patient made an uneventful convalescence and was discharged from the hospital fifteen days after operation.

The pathologic diagnosis was perforated ulcer of the pyloric region, with pancreatic tissue embedded and attached to the serosal layer of the stomach and duodenum.



This case is cited to illustrate the significance of an accurate history in the diagnosis of chronic pancreatitis associated with duodenal ulcer. On the tenth postoperative day the son-in-law informed me that the patient was a Christian scientist and had never admitted the pain or discomfort which she had suffered between the first attack of pain and that which she complained of three months before consulting me. The patient, according to his statement, had had epigastric distress and vague abdominal pain for a year preceding the acute attack of pain which occurred in July 1931 and persistent discomfort from that time until her operation.

CASE 2.—A man, aged 38, entered the clinic for patients with gastric disease of the Fourth Division of the Bellevue Hospital in March 1930 with a history of severe pain in the upper part of the abdomen and of operation for ulcer. From 1920 to 1925 the patient had had vague symptoms in the upper part of the abdomen, with pain, gas and indigestion. He entered the Jersey City Hospital in March 1925, where roentgenograms were taken of the stomach. A report of pylorospasm was made, and operation was performed. The stomach and duodenum were pronounced normal, but an appendectomy was performed for chronic appendicitis. He improved for a period of about six months, and then symptoms similar to those that he had had prior to operation returned. These symptoms persisted until March 1929, when the patient had severe pain, collapsed on the street and was taken to the Jewish Hospital of Brooklyn, where he was operated on for perforated ulcer of the stomach. At that time the ulcer could not be closed, as it had perforated posteriorly. A gastro-enterostomy was done; drains were inserted, and the patient made an uneventful convalescence. Within four months after this operation he began to have severe pain in the upper part of the abdomen. He was under the care of his own physician for several months, but without improvement.

*Course of Illness.*—At the time of entering the clinic roentgenograms were taken which revealed a gastrojejunal ulcer in the efferent loop of the jejunum but no retention in the stomach at the end of six hours. The patient was under treatment in the clinic through the year 1930 until January 1931. A reexamination of the stomach and duodenum in November 1930 revealed a gastrojejunal ulcer. The patient had shown some improvement; he discontinued treatment at the clinic, and returned to his private physician, under whose care he remained until August 1932. At that time he returned to this clinic, complaining of severe pain in the abdomen which radiated through to the back and necessitated the taking of morphine and codeine for sleep. Roentgenographic examination on Sept. 10, 1932, revealed a gastrojejunal ulcer. Owing to the severe pain in the back which the patient was suffering, a clinical diagnosis was made of gastrojejunal ulcer perforating into the pancreas and chronic pancreatitis. Operation was performed on Oct. 10, 1932, and a gastrojejunal ulcer perforating into the pancreas was observed; the duodenum was also plastered against the head of the pancreas, and the entire head and body of the pancreas were enlarged and indurated. The gastro-enterostomy was dissociated, and the stomach was closed with no. 1 chromic gut, three layers of sutures being used. The ulcer of the jejunum was so adherent to the pancreas that it necessitated a resection of 5 inches (12.7 cm.) of the jejunum with an end-to-end anastomosis of the jejunum. From palpation and inspection of the duodenum and the pyloric region of the stomach, the ulcer was considered inactive, and owing to the poor condition of the patient it was considered inadvisable to

make a resection at that time. The patient made an uneventful convalescence and left the hospital fourteen days later. He remained under observation in the clinic, and for the first year after his operation he was free from symptoms. In July 1933 he again complained of pain in the abdomen which prevented him from sleeping. He had to take codeine at intervals to obtain sleep. Roentgenograms taken in July 1933 revealed deformity of the duodenum with retention for six hours. The patient was given various medicaments, including Saunders' vaccine, Synadol and gastric mucin, but without improvement. In June 1934 he complained of excruciating pain in his back; he had no abdominal pain and stated that he felt well except for the pain through the lumbar region, which was so severe that his family physician had to administer morphine to obtain relief. The patient was referred by the family physician to the Post-Graduate Medical School and Hospital on June 3, 1934. Examination revealed tenderness in the region over both kidneys and no abdominal tenderness. A diagnosis of chronic pancreatitis resulting from the preexisting duodenal ulcer was made. The pain in his back was so severe that roentgenograms were taken of the genito-urinary tract on June 4 to rule out the possibility of stone. A series of roentgenograms of the gastro-intestinal tract was taken, and a diagnosis of pyloric obstruction due to duodenal ulcer was made. Operation was performed on June 9 with a preoperative diagnosis of ulcer of the posterior part of the duodenum and chronic pancreatitis. After the abdomen was opened the duodenum was seen to be adherent to the head of the pancreas, the head of the pancreas being the size of an orange. A gastric resection was made with the removal of 75 per cent of the stomach and of  $1\frac{1}{2}$  inches (3.81 cm.) of the duodenum. An ulcer of the posterior part of the duodenum the size of a 25 cent piece had perforated the entire wall of the duodenum, the base of the ulcer being formed by the head of the pancreas. There was an erosion at the head of the pancreas the length of the distal phalanx of one's little finger and from about 3 to 5 mm. deep. The patient died three days later of peritonitis.

Autopsy revealed peritonitis which had originated in the lesser peritoneal sac, an enlarged pancreas and chronic pancreatitis. The pathologist, Dr. Rabson, considered the chronic pancreatitis as the etiologic factor in the production of the peritonitis of which the patient died.

I wish to call attention to the fact that the patient's pain and symptoms were all referable to the back and that the pain was so severe that it necessitated the use of morphine. The family physician considered that the patient at the time of his admission to the hospital was suffering from a stone in the kidney and that his symptoms were not due to the preexisting ulcer. The interns at the hospital thought that the patient was probably an addict to drugs, as it was necessary to give him morphine for the relief of pain. The observations at operation and at autopsy clearly indicated that the only existing pathologic condition was the perforated duodenal ulcer with chronic pancreatitis.

The management of a bleeding peptic ulcer is one of the most difficult complications which one encounters. The cases of the patients with gross hemorrhage treated medically and surgically in the Fourth Surgical Division were reviewed. These cases were reported,<sup>7</sup> and a

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7. Hinton, J. W.: Massive Hemorrhage in Peptic Ulcer: Report of Eighty-Seven Cases, *Ann. Surg.* **101**:856 (March) 1935.

special grouping of eighty-seven cases of gross hemorrhage was made. It seems worth while to give the classification of cases of hemorrhage as I grouped them on the basis of my study.

Group 1 comprised sixteen cases of hemorrhage occurring in patients with peptic ulcer under competent medical management; group 2, eleven cases of hemorrhage in which operation for acute perforation or chronic ulcer had been performed and in which the catastrophe of hemorrhage had not occurred until months or years after operation; group 3, five cases of hemorrhage occurring in ulcers that had previously been operated on for hemorrhage, in which the patient continued to have recurring hemorrhage after operation; group 4, seventeen cases of severe hemorrhage which occurred in patients with normal histories or with short histories of gastric symptoms, who did not know they had ulcer until the hemorrhage occurred, and group 5, thirty-eight cases in which the patients were admitted with hemorrhage and a long history of symptomatology of ulcer, but without regulated medical management.

From this classification of cases of gross hemorrhage it can be seen that prolonged medical management of a patient who has had one severe hemorrhage after being under adequate medical management is merely inviting another such catastrophe, and for that reason one does not consider prolonged medical treatment for this group of patients.

CASE 3.—A man, aged 38, seen at his home on Jan. 11, 1931, gave a history of having been treated for ulcer of the duodenum for the two and a half years before I saw him. Two days before consultation with me he had had a slight cold and some abdominal discomfort. He had been practically free from symptoms for one year prior to that time. The night before I saw him he passed dark blood by rectum, and on the morning of my visit he had vomited a large quantity of blood. He was immediately transferred to the Post-Graduate Hospital and given a transfusion of 600 cc. of blood. On January 16 he was operated on, and an ulcer was noted in the first portion of the duodenum. Excision of the ulcer and posterior gastro-enterostomy were then performed, with no. 1 chromic gut used for sutures. The gallbladder was normal, but an appendectomy was performed for chronic appendicitis; the abdomen was closed in anatomic layers. The patient made an uneventful convalescence. The pathologic diagnosis was chronic appendicitis and duodenal ulcer with a tendency to heal. The patient left the hospital twenty-two days after the operation.

This patient has been under constant observation since his operation in January 1931; he has been well since that time and has had no abdominal pain or hemorrhage. I wish to call attention to the fact that the patient had been under a strict and regulated medical regimen and had been free from symptoms for one year prior to the sudden, severe hemorrhage which necessitated hospitalization and operation.

Complications following operation for peptic ulcer include hemorrhage, acute perforation of a peptic or gastrojejunal ulcer, chronic gastrojejunal ulcer and gastrojejunal fistula resulting from the formation of gastrojejunal ulcer.

In considering gross hemorrhage that follows operation for peptic ulcer it is best to consider the classification of hemorrhage given in this paper. This sequela is serious, and the management of each case has to be decided from its course. As a rule reoperations on the patients that have had hemorrhage after the first operation give poor results.

The following case is cited because, on the basis of my classification, the original operation should not have been done.

CASE 4.—A man, aged 38, was seen on Sept. 15, 1934, complaining of slight pain in the epigastrium for four days prior to his admission and of having had hemorrhages from the stomach during the last three and a half years.

The patient stated that in February 1931 he had had a severe gastric hemorrhage, for which he was treated in the Misericordia Hospital of Philadelphia for seven weeks. He was given a transfusion at that time and was later operated on for a duodenal ulcer. At that time a plastic operation was performed on the duodenum, and the patient made an uneventful convalescence, except that a small hernia developed in the upper part of the incision. About one year later (the exact date he did not recall but thought it was about March or April 1932) he had another hemorrhage from the stomach; neither at this time nor during the first hemorrhage did he vomit blood, passing it all by bowel. He had no pain during the time between the operation and the second hemorrhage; he had had no symptoms referable to the stomach preceding the first hemorrhage, but he suddenly collapsed as the result of the hemorrhage. He was treated medically at this time. Approximately one year after this hemorrhage, in the spring of 1933, he had another hemorrhage; it was also from the bowel. He was again treated medically and was well until February 1934, when he again had a hemorrhage from the stomach. He had had no pain or abdominal discomfort until approximately ten days before consulting me, and the slight abdominal pain became a little more severe four days before the visit. At the time of my examination he had a definite ventral hernia and slight epigastric tenderness. The blood count showed 4,600,000 red cells, 87 per cent hemoglobin, 9,000 leukocytes and 67 per cent polymorphonuclears. He was given a Sippy diet as planned for the third week and an injection of Saunders' vaccine, and was advised to return two days later for roentgenography. On the same night after he consulted me he had a slight hemorrhage with a dark stool. He was referred immediately for roentgen examination, which revealed an ulcer of the posterior part of the duodenum. Dr. Spillman reported that because of a persistent notch on the inferior surface of the cap, which is characteristic of duodenal ulcer, he thought the patient should be operated on, as the lesion was uncomfortably close to the superior pancreaticoduodenal artery.

This patient undoubtedly had two ulcers at the time of his first operation, one on the anterior and one on the posterior portion of the duodenum. The plastic operation eradicated the ulcer on the anterior surface, but that on the posterior surface remained. In view of the recurring hemorrhages and the location of the ulcer, the patient was

advised to have a second operation, as it was feared that he might have a sudden fatal hemorrhage. Of course, it would be necessary to make a subtotal resection in this case.

The occurrence of perforated ulcers of the stomach and duodenum apparently is on the increase,<sup>8</sup> and the accepted method of management in most clinics is simple closure and the reservation of more radical procedures until a later date. Therefore, it is natural to expect that in a reasonable number of these patients reperforation will occur, as is occasionally seen.

CASE 5.—A man, aged 37, was first seen in February 1927, complaining of abdominal pain occurring after meals and occasionally at about 2 or 3 a. m. for from six to nine months. The patient stated that for about eight or nine months before consulting me his symptoms had grown gradually worse. The physical examination revealed epigastric tenderness; otherwise abdominal examination revealed nothing abnormal. A diagnosis of duodenal ulcer was made. Roentgenograms taken at the Post-Graduate Hospital on Feb. 18, 1927, revealed a duodenal ulcer without six hour retention. The patient did well under medical treatment until Jan. 18, 1929, when he was seized with severe abdominal pain. A diagnosis of perforated duodenal ulcer was made, and he was operated on at the New York Post-Graduate Medical School and Hospital. Perforation of a duodenal ulcer was noted, and a Horsley pyloroplasty and appendectomy were done. The patient made an uneventful convalescence and was discharged on the fifteenth postoperative day. He was free from symptoms until Sept. 29, 1929, when he was awakened at about 2 a. m. with severe abdominal pain and was taken immediately to the Post-Graduate Hospital with a diagnosis of perforated duodenal ulcer. He was operated on, and a perforation of a duodenal ulcer was observed. Excision of the ulcer was made, and the duodenum was closed with no. 1 chromic gut. Cholecystectomy was also done, and the abdomen was closed in anatomic layers. The patient made an uneventful convalescence and was discharged from the hospital on the sixteenth postoperative day. He remained well and free from symptoms until November 1931, when he began to have epigastric distress, which persisted for about six weeks. On Dec. 2, 1931, he consulted me at my office. The physical examination revealed nothing abnormal, although he complained of slight epigastric distress. Immediately on leaving my office and returning to his residence, he had severe abdominal pain and was taken immediately to the Post-Graduate Hospital, where he was operated on for a third perforated duodenal ulcer. Excision of the ulcer was made, and the abdomen was closed in anatomic layers. The patient again made an uneventful convalescence and was discharged from the hospital on the seventeenth postoperative day. After this operation he was free from symptoms for six months, but from September 1932 he had slight epigastric pain and was under constant medical treatment. On Dec. 30, 1932, he was awakened by a feeling of nausea and had a severe gastric hemorrhage. He was again admitted to the New York Post-Graduate Medical School and Hospital and received a transfusion of 750 cc. of blood on three occasions. He remained in the hospital three weeks. After this hemorrhage he continued to have slight epigastric distress and was never entirely free from symptoms through the year 1933, although he

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8. Hinton, J. W.: Incidence of Peptic Ulcer and Its Complications, *Am. J. Surg.* 20:102 (April) 1933.

remained on a strict Sippy regimen, did not use alcohol or tobacco and was careful of his hours. In January 1934 he was having severe pain. Roentgenograms taken at that time revealed a duodenal ulcer, and he entered St. Luke's Hospital on Feb. 13, 1934, where he was operated on for duodenal ulcer. Operation revealed a duodenal ulcer on the superior portion of the duodenum; subtotal resection was performed with the removal of 75 per cent of the stomach, and an anticollic anastomosis without entero-enterostomy was made. The patient made an uneventful convalescence during the first three days; the abdomen then became distended, and he was critically ill for five days. He seemed to improve and to be out of danger, but he died suddenly on the twelfth postoperative day. Autopsy revealed complete necrosis of the pancreas and hemorrhage from the pancreatoduodenal artery.

This case is cited to illustrate the tendency of ulcer to recur although the ulcer has been completely excised in previous operations.

Acute perforation of a gastrojejunal ulcer is seen in cases in which a diagnosis of ulcer has never been suspected, and the following case illustrates a late marginal ulcer.

CASE 6.—A man, aged 41, was admitted to the Bellevue Hospital on Nov. 15, 1933, with a history of severe epigastric pain of a few hours' duration. The patient gave a history of having been operated on at the Gouverneur Hospital in October 1920 for ulcer of the stomach. The records from that institution revealed that he had had a posterior gastro-enterostomy for pyloric ulcer on Oct. 2, 1920, and that he had given a history of epigastric pain for two years preceding the operation. After the operation he had had slight attacks of epigastric distress, but, generally speaking, he had been in good health and considered himself cured of the ulcer. At the time of his admission he was suffering from severe abdominal pain of a few hours' duration. Examination revealed marked rigidity and tenderness of the abdomen, and a diagnosis of perforated ulcer was made. A laparotomy revealed a perforated gastrojejunal ulcer, the perforation being on the stoma. A simple closure of the perforation was made, and the patient made an uneventful convalescence and was discharged from the hospital on the nineteenth day. This patient has been in the clinic of the Fourth Division of the hospital since his discharge. He has been essentially free from symptoms, and roentgenograms taken on Aug. 6, 1934, revealed a gastro-enterostomy opening which functioned normally. However, slight tenderness over the stoma and defective filling at the base of the duodenum with a retention of six hours, characteristic of duodenal ulcer, were noted.

Chronic gastrojejunal ulcer does occur after both gastro-enterostomy and subtotal resection. The incidence after gastro-enterostomy is much higher than is admitted in most clinics, provided one is careful to observe these patients over a period of years. On the basis of observation in this clinic, the frequency of 2 or 3 per cent for marginal ulcer after gastro-enterostomy, as reported from most clinics, in no way expresses the true incidence of this sequela. According to the observations of my associates and me, gastrojejunal ulcer occurred in 16.4 per cent of eighty-five patients with gastro-enterostomy<sup>9</sup> who have been

9. Church, Reynold, and Hinton, J. W.: A Study of Six Hundred and Seventy-One Cases of Peptic Ulcer with Special Emphasis on One Hundred and Fourteen Post Operated Cases, New York State J. Med., to be published.

under observation in this clinic during the past five years. It is worth while to remember that the longer the patients are under observation, the higher the incidence of gastrojejunal ulcer will be.

Gastrojejunal-colic fistula is not unusual; it results from the formation of a gastrojejunal ulcer on the anterior line of the anastomosis of the stoma, the ulcer actually being located on the jejunum. The transverse colon becomes adherent to the ulcerated area, and the ulcer gradually erodes and perforates the entire wall of the jejunum and later that of the transverse colon. At first the opening is relatively small, but as the condition progresses the opening becomes larger, and the patient suffers from extreme diarrhea and emaciation, associated with abdominal pain on the left side.

In the following case a spontaneous gastrocolic fistula developed while the patient was under medical treatment.

CASE 7.—A woman, aged 60, was first seen at the clinic on Dec. 4, 1930, with a history of epigastric pain and indigestion for a period of ten years.

The patient stated that for a period of ten years she had had slight epigastric distress and gas; for eight months prior to her admission she had had severe pain, and for the last six months she had been vomiting several times a week. Roentgenograms taken Oct. 30, 1930, before admission to the clinic, revealed an ulcer of the lesser curvature in the pars media, with retention for six hours of two thirds of the motor meal. The diagnosis was that of gastric ulcer.

The physical examination revealed a rather poorly nourished woman weighing 111 pounds (50.3 Kg.). The Wassermann test gave a 4 plus reaction. It was believed probable that the patient had a syphilitic ulcer of the stomach. An operation was advised, but she refused to permit it; therefore she was put on an ambulatory medical regimen, as her husband was paralyzed and she refused to enter the hospital for rest in bed. The patient was fairly conscientious and remained under the care of physicians at the clinic until Jan. 26, 1933. During her period of treatment her weight remained the same, between 110 and 115 pounds (49.9 and 52.1 Kg.). A follow-up visit to the home on June 8, 1933, failed to reveal the patient at the address which had been given. No information could be ascertained as to her whereabouts. The patient had numerous roentgen examinations while under care at the clinic, all of which revealed the same condition as had the first examination. She was examined on March 2 and June 15, 1931; on Jan. 7, May 4 and Oct. 16, 1932, and on Jan. 30, 1933, on all of which occasions a gastric lesion was revealed with a six hour retention of from one half to three fourths of the motor meal. During the period under which she was under treatment at the clinic, she was receiving antisyphilitic treatment in the dermatologic department of the Bellevue Hospital; the Wassermann reaction remained positive while she was under antisyphilitic treatment. The patient was brought into the hospital on July 16, 1934, as presenting an emergency case, and was admitted to the Fourth Medical Division. At that time she gave a history of diarrhea for two or three months and stated also that she had had diarrhea for four years. I wish to call attention to the incorrectness of this statement, for she never complained of diarrhea during the three years that she was under constant treatment in the clinic. The diarrhea was of moderate severity with from two to four movements of the bowels

a day. Roentgen examination and a series of roentgenograms of the gastro-intestinal tract made on July 21, 1934, revealed a gastrocolic fistula. Figure 1 shows the entire meal lying in the colon immediately after the barium was administered. This picture should be contrasted with figure 2, taken at the time of the patient's admission to the clinic in October 1930, which reveals a large gastric ulcer and

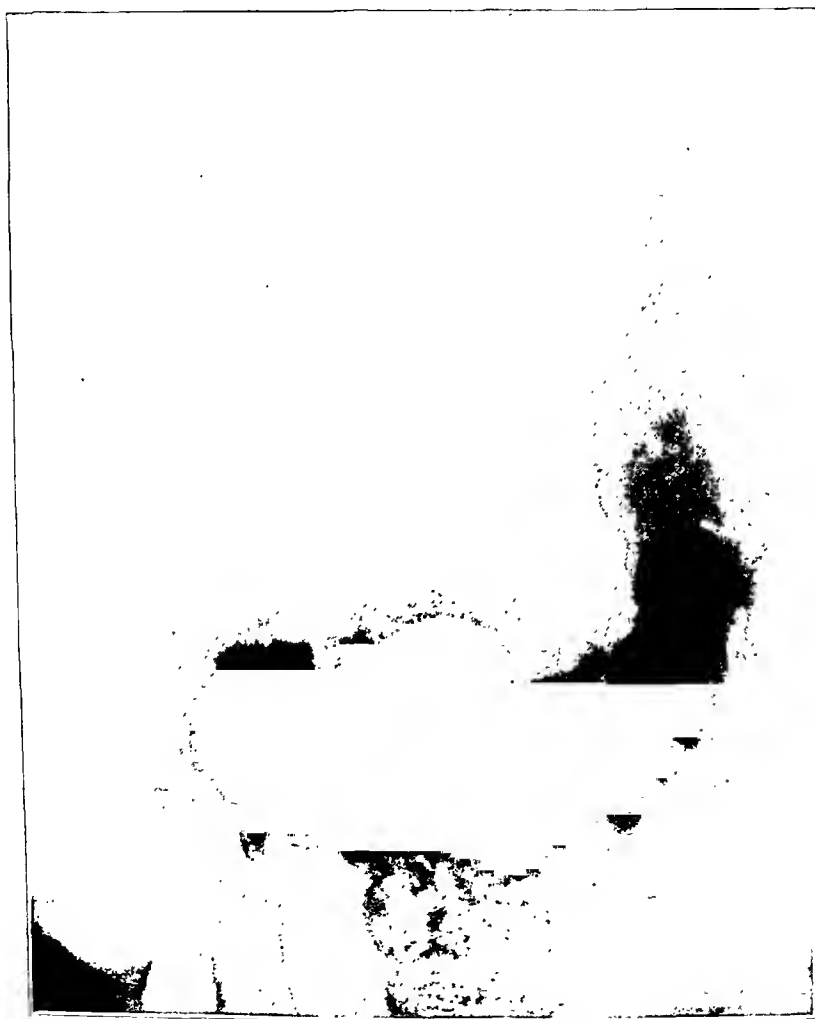


Fig. 1.—Roentgenogram taken July 21, 1934, immediately after administration of the barium meal which lies entirely in the colon.

marked retention of the motor meal. The patient was in a critical condition; she refused to undergo operation and died on Aug. 3, 1934. Autopsy revealed a gastrocolic fistula, which is illustrated in figure 3. The fistula was spontaneous and, in all probability, syphilitic, although spirochetes were not demonstrated and no other evidence of syphilis was seen at the time of autopsy.



This case illustrates an unusual complication of gastric ulcer occurring while the patient was under medical care. The patient had been advised to undergo operation, but she refused to consider surgical intervention.

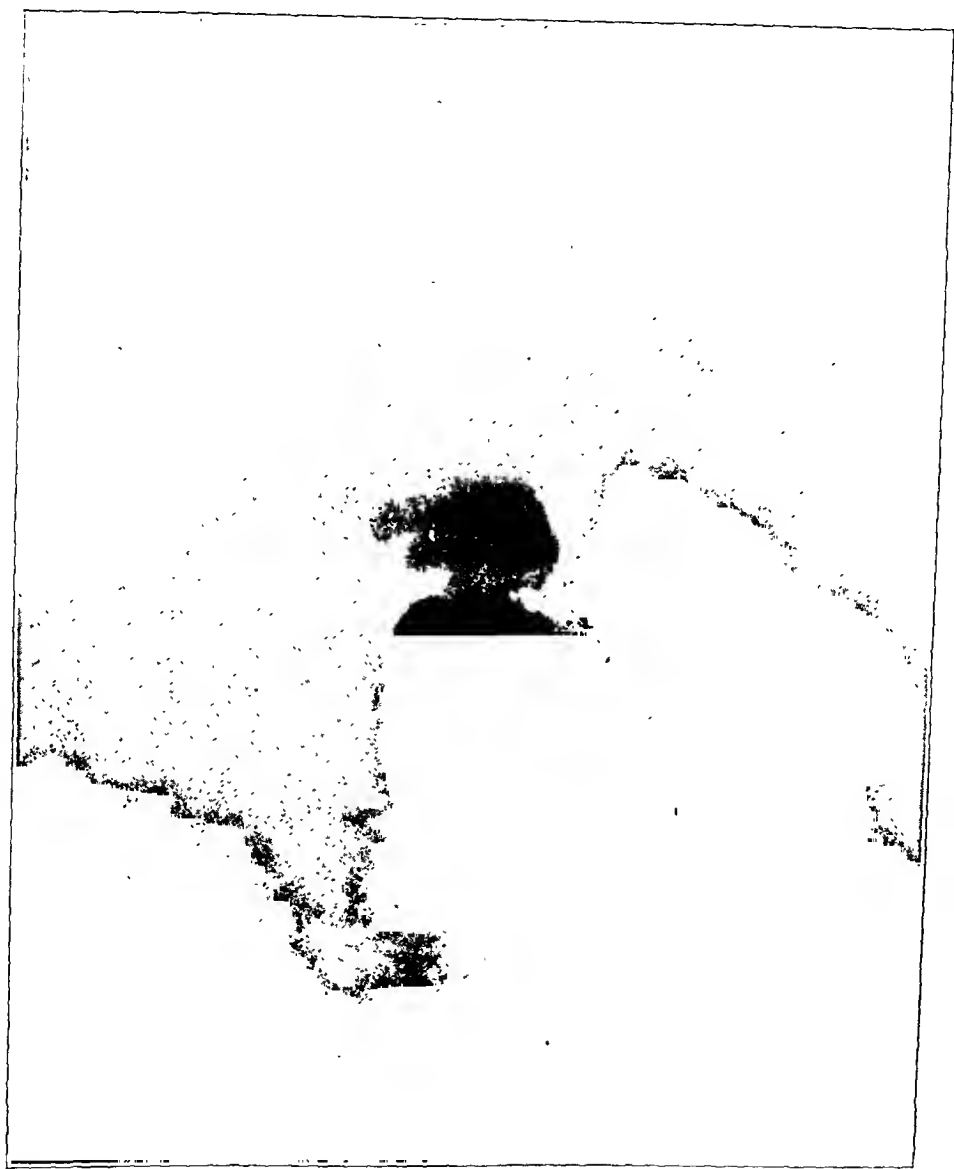


Fig. 2.—Roentgenograms taken in October 1930, showing gastric ulcer of the lesser curvature and retention of two thirds of the motor meal in the stomach.

As physicians are interested in the prevention of complications which may occur in patients suffering from peptic ulcer, they are forced to revise some of the accepted indications for operation. The internist in the past and at present usually accepts two conditions as true indications for operation—first, a gastric lesion, because of his fear of malign-

nant degeneration, and, second, gastric retention of from 50 to 75 per cent of the meal at the end of six hours. Unfortunately, these two conditions are not true indications for surgical treatment, and in the majority of instances gastric lesions respond to medical management much more readily than duodenal lesions. Also in 75 or 80 per cent of the patients suffering from gastric retention of 50 or 75 per cent of the meal at the end of six hours, the stomach will completely empty under proper medical management. On the other hand, pain which is persistent without periodicity is a true indication for referring patients for surgical treatment. It is a patient of this type that the internist

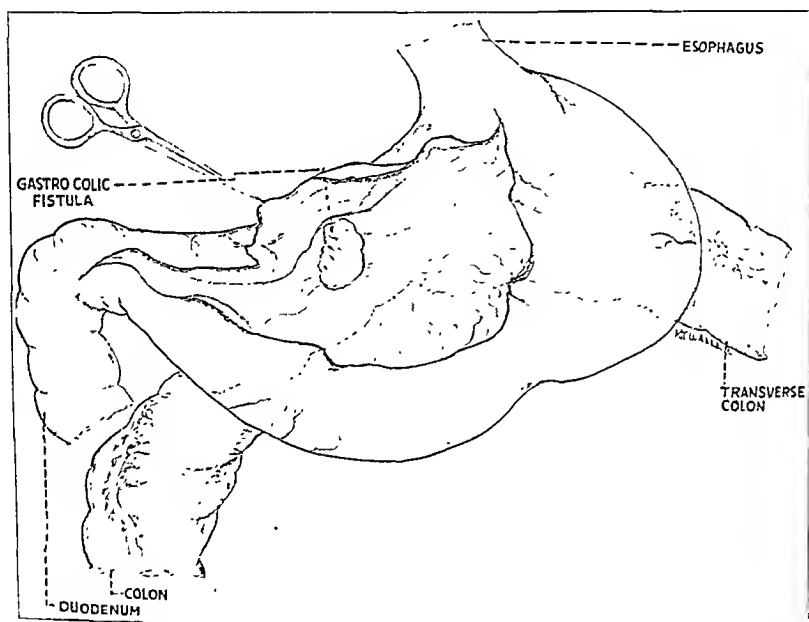


Fig. 3.—Drawing showing the position of the gastrocolic fistula.

frequently hesitates to submit to surgical treatment, believing that, since the stomach empties normally and there is no pyloric obstruction, the patient will ultimately respond to medical management. This is not true, and a patient of this type, as has been stated before, is suffering from an associated lesion, which is usually chronic pancreatitis. When the pancreas becomes involved in an associated infection the medical management should be immediately discontinued and the patient referred for operation.

A discussion of the incidence of gastrojejunal ulcer elicits considerable comment and difference of opinion from physicians in all the large clinics in the country. It can only be stated that, on the basis of

observations in this clinic, it is believed that the incidence of 16.4 per cent in cases of gastrojejunal ulcer after gastro-enterostomy is an underestimation, rather than an overestimation, of the exact frequency of occurrence of this complication. A large number of patients are returning with gastrojejunal lesions as well as with gross hemorrhage as the clinic grows older.

There is no condition in medicine at present in which clinical judgment plays such an important part in the selection of the method of treatment for the patient as it does in peptic ulcer. Whether the treatment should be medical or surgical is a decision that is based to a great extent on clinical experience. Many of the mistakes that are made and the poor results that are obtained from medical and surgical management are due to the physician's relying too closely on the laboratory findings of hyperacidity and on the report, based on roentgenologic findings, of normal evacuation of the stomach at the end of six hours.

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# FIFTY-SEVENTH REPORT OF PROGRESS IN ORTHOPEDIC SURGERY

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## CONGENITAL DEFORMITIES

*Congenital Dislocation of the Hip.*—In a detailed statistical study of 387 cases of congenital dislocation of the hip, representing 501 dislocated hips treated during the period of 1915 to 1933, Steindler and his co-workers<sup>1</sup> reported the results of both closed and open methods of reduction. They concluded that the results of the closed method were not as conclusively satisfactory as those reported by other authors and that the results became definitely worse with duration of the period of observation. They expressed the belief that in order to be accurate, the end-results should be regarded as significant only after full growth has been obtained. The authors used open reduction as a supplementary method and therefore did not attempt to compare the results obtained by open with those obtained by closed reduction. They considered the indications for open reduction to be the inability to reduce or to maintain reduction by closed methods. The upper age limit for open reduction they considered to be 11 years. The authors have included an excellent statistical study which is too detailed for inclusion

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This report of progress is based on a review of 136 articles selected from 202 titles appearing in medical publications approximately between Nov. 3, 1934, and Feb. 22, 1935. Only those which seemed to represent progress were chosen for review.

1. Steindler, A.; Kulowski, J., and Freund, E.: *Congenital Dislocation of the Hip: Statistical Analysis*, J. A. M. A. 104:302 (Jan. 26) 1935.

in this summary but should be read by all who are interested in the treatment of congenital dislocation of the hip.

#### POLIOMYELITIS

*Convalescent Serum in the Treatment of Poliomyelitis in the Preparalytic Stage.*—Fischer<sup>2</sup> studied 447 cases of poliomyelitis in which treatment with serum from convalescent patients was used and 102 control cases occurring in New York City in 1931. The condition three weeks after onset was compared with the end-result six months later, the data being given in tables. Fischer expressed the belief that the value of convalescent serum in the treatment of poliomyelitis in the preparalytic stage was not definitely proved because, in spite of every effort to obtain comparable data, it was not possible to do so. The data presented demonstrated that the outcome for the patients given convalescent serum was no better than, if as good, as that for the untreated ones. While in the control patients the attack of poliomyelitis was probably somewhat milder, it appeared that no advantage was shown by the other groups. There was no proof that a physician was depriving his patient of an equal chance for complete recovery by not administering convalescent serum.

*A Study of 410 Patients at the Philadelphia Hospital for Contagious Diseases During the Summer and Fall of 1932.*—Four hundred and ten patients with conditions suspected of being poliomyelitis were admitted to the Philadelphia Hospital for Contagious Diseases in 1932. In 304 cases (74.1 per cent) the diagnosis was verified. Two hundred and fifty-four patients (68.5 per cent) received serum; 124 of these showed weakness or paralysis on admission, but at the time of discharge the number of patients showing such symptoms had increased to 154. Fifty patients (16.5 per cent) received no serum on admission; of these 28 on admission and 38 at discharge showed weakness or paralysis. Lucchesi<sup>3</sup> concluded that convalescent serum had little or no value in the prevention of paralysis.

*A Successful Method for Vaccination Against Acute Anterior Poliomyelitis.*—Kolmer and his associates<sup>4</sup> succeeded in preparing from the spinal cords of monkeys an attenuated virus of anterior poliomyelitis; from this a vaccine was obtained and used on 25 children. In 21 of

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2. Fischer, A. E.: Human Convalescent Serum in Treatment of Preparalytic Poliomyelitis; Comparison of 447 Treated and 102 Control Patients in New York City in 1931, *Am. J. Dis. Child.* **48**:481 (Sept.) 1934.

3. Lucchesi, P. F.: *Am. J. M. Sc.* **188**:515, 1934.

4. Kolmer, J. A.; Klugh, G. F., Jr., and Rue, Anna M.: Successful Method for Vaccination Against Acute Anterior Poliomyelitis, *J. A. M. A.* **104**:546 (Feb. 9) 1935.

the 25 patients increase in the antibody content of the blood was shown by titration after the inoculations. The authors considered the vaccine as entirely safe for use and expressed the belief that the amount of the antibodies formed is comparable to that found in the blood of naturally immune subjects. The duration of the immunity was unknown, but it had been found to last for two days in monkeys. Kolmer and his co-workers considered that their vaccine was now ready for use in clinics as a protective agent and should be used particularly during the time of epidemics.

[ED. NOTE.—The results of this work seem to be really noteworthy and certainly should be given a thoroughly controlled trial at the earliest opportunity.]

#### TUBERCULOSIS

*Tuberculosis of the Spine in Children.*—From a study of 89 children suffering from tuberculosis of the spine Cave<sup>5</sup> concluded that probably the most important factor in determining the degree of deformity was the amount of destruction which occurred in the posterior supporting structures (pedicles and laminae). He stated that rapid progression of deformation may be prognosticated by finding mobile spinous processes in the involved area. From the classification of Doub and Badgley, most rapid destruction was observed in the intervertebral type and the most marked deformity was found in the central type. In this series there were five double lesions, all of which occurred in the lower dorsal and lumbar regions. An abscess containing calcium was almost a certain sign of tuberculosis. Biopsy, culture and inoculation of guinea-pigs were the methods used in making a diagnosis. In 70 of the 89 cases roentgenograms showed an abscess. Treatment in the acute cases consisted in recumbency on a Bradford frame with gradual hyperextension and, later, application of a plaster jacket. The average period of recumbency was thirty-three months for the patients who had not undergone operation; for those who were operated on it was thirty-nine months. Operative fusion of the spine was carried out when deformity increased in spite of hyperextension. Cave stated that every attempt should be made to prevent deformity and that fusion may insure healing without apposition of adjacent vertebral bodies. The end-results in the 89 cases were classified as follows: excellent, 18; good, 26; fair, 10; poor, 10. Twenty of the patients died, and in 5 cases the nature of the end-results was unknown.

*Tuberculous Tenosynovitis of the Hand.*—In a carefully prepared monographic article on tuberculous tenosynovitis of the hand Mason<sup>6</sup> outlined the symptoms, clinical course and pathologic changes in, and

5. Cave, E. F.: New England J. Med. **211**:578, 1934.

6. Mason, M. L.: Surg., Gynec. & Obst. **59**:363, 1934.

prognosis of, the disease. He concluded that the best treatment was the surgical excision of the diseased tissue, including the visceral layer of the tendon sheath. In some instances diseased portions of the tendons themselves had to be sacrificed. The optimum location for incision, the operative technic and the after-care were described in detail.

#### OSTEOMYELITIS

*The Stewart Treatment for Osteomyelitis.*—Kline<sup>7</sup> reviewed 5 cases, 4 of chronic osteomyelitis lasting for periods varying from six months to eighteen years and 1 of a severely infected wound. Healing was complete in every case in from thirty to seventy-five days. The Stewart<sup>8</sup> method of treatment called for a 0.25 per cent solution of trinitrophenol prepared with distilled water to which glycerin was added to the amount of 8 per cent. The solution was sprayed into small wounds, poured into large ones and forced through fistulous tracts with a soft rubber catheter and a 5 cc. Luer syringe. Immediately after application of the trinitrophenol solution an autoclaved suspension consisting of 20 Gm. of calcium carbonate and 215 cc. of distilled water was applied to the wound. Kline found that granulation tissue formed promptly, purulent exudate was reduced, healing was rapid, pain and discomfort were minimized and the residual scar was less marked.

*Acute Osteomyelitis.*—Fraser<sup>9</sup> regarded acute staphylococcic osteomyelitis as a local manifestation of a general local reaction, calling into being strong antibacterial influences, which were efficient in counteracting the general sepsis. He advocated a modified form of Starr's operation. It was suggested that the localization of infection in the metaphyses of long bones may be due to the fact that these areas are rich in reticulo-endothelial tissue, which is one of the most important defensive mechanisms of the body against general infection.

*Nature and Treatment of Acute Osteomyelitis.*—Conservative methods in the treatment of acute osteomyelitis were advocated by Holman,<sup>10</sup> who considered that this condition was merely a local manifestation of systemic infection. Expectant treatment and immobilization were used until there was definite evidence of the formation of pus. In the majority of cases simple incision of the periosteum was all that was necessary at the primary operation. While sequestrums were frequently formed and had to be removed at a second operation, in some cases they were absorbed. Only one death occurred in a group of 29 patients treated by the conservative method.

7. Kline, L. B.: *Mil. Surgeon* 75:251, 1934.

8. Stewart, M. N.: *Surg., Gynec. & Obst.* 58:155, 1934.

9. Fraser, J.: *Brit. M. J.* 2:539, 1934.

10. Holman, C. C.: *Lancet* 2:867, 1934.

[ED. NOTE.—There is a growing conviction that in cases of osteomyelitis and other infections the patient should not be forgotten in attempts to treat local manifestations of a systemic disease. The resistance of the patient and the reparative forces of the body should be helped and not retarded by the therapeutic measures used.]

#### CHRONIC ARTHROPATHIES

*Some Metabolic and Nutritional Aspects of Chronic Arthritis.*—Pemberton<sup>11</sup> in a general paper stressed the importance of a balanced diet, particularly for relief of edema about the joints. He stated that edema disappeared with a diet with a low carbohydrate and a high protein content. Three and six-tenths grams of water was retained in the body for every gram of carbohydrate stored. A diet with a high protein content required available water for the elimination of protein metabolites. A diminution of pain was usually found to accompany a negative water balance. In the majority of advanced cases of chronic arthritis dysfunctions of the gastro-intestinal tract were present. Pemberton stated that chronic arthritis is a generalized disease with certain "prodromes." Coordination of various lines of therapy based on sound physiologic premises should control the disease in 80 per cent of the cases.

*Rheumatoid Arthritis and Its Treatment with Gold Salts.*—Forrestier<sup>12</sup> reported that from 70 to 80 per cent of patients with rheumatoid arthritis had responded well to therapy with gold salts. He observed a series of 500 cases. The best results were obtained when treatment was given in the early stages, but in 12 cases of chronic arthritis with irreducible ankylosis of one or many joints, reduction under anesthesia was made possible, without any subsequent inflammatory reactions, when a preliminary course of injections of gold salts was administered. Forrestier advanced the hypothesis that the development of rheumatoid arthritis is accompanied by tuberculous infections but that it requires another infective element, such as tonsils or teeth, to provide it.

[ED. NOTE.—One of the editors is familiar with the work reported by Forrestier. Many other measures, both medical and orthopedic, are used by him in the treatment of this condition. The use of heavy metals in colloidal suspension probably has a definite but limited application in the treatment of chronic arthritis, particularly in patients past middle life, in whom stimulation of the reticulo-endothelial system seems at times to be indicated.]

11. Pemberton, R.: *Am. J. Digest. Dis. & Nutrition* 1:438, 1934.

12. Forrestier, J.: *Lancet* 2:646, 1934.



*Neuropathic Disease of the Joints.*—Bergmann<sup>13</sup> expressed the opinion that the pathologic alterations in neuro-arthropathies are understandable on the basis only of trophic disturbances. He expressed the belief that mechanical influences play only a small rôle in the development of the lesion and that antisiphilitic treatment is of some value in treatment in the early stages of the disease. Early diagnosis is difficult. He stated that he had no experience with operative fusion of the knee but that on the basis of Oehlecker's and Payr's experiences he was inclined to advise against such procedures.

[ED. NOTE.—Early operative fusion of the knee in tabetic patients has been found to be a satisfactory procedure in the experience of one of the editors. The histopathologic changes in the joints in patients with neuropathic diseases as outlined by Moritz suggest that trauma plays a considerable rôle in the development of the disorder in the joints.]

#### THE SPINE

*Treatment of Kyphosis in Adolescent Patients.*—Calvé<sup>14</sup> stated that the spontaneous natural curves formed to compensate for kyphosis in adolescent patients are unsatisfactory because pain follows in the lumbar area of hyperextension. Therapeutic compensation consists in bringing about extension curves immediately above and below the area of kyphosis. The method that he advocated to secure therapeutic compensation was recumbency in a position of hyperextension on a shaped plaster bed. He stated that this method is better than the wearing of plaster jackets, for it permits the application of physical therapy to the muscles of the trunk, on the strength of which the maintenance of the new position depends.

[ED. NOTE.—The development of compensatory curves in kyphosis in adolescent patients, frequently called epiphysitis of the spine in America, is not always necessary. The procedures used to correct the kyphosis in patients with tuberculosis or chronic arthritis of the spine are frequently effective in the treatment of kyphosis in adolescent patients.]

#### PERIPHERAL VASCULAR DISTURBANCES

*Passive Vascular Exercises.*—The treatment of obliterative arterial diseases by a new "Pavaex" apparatus was described by Herrmann and Reid.<sup>15</sup> The limb was encased in a machine applying rhythmic alterations of pressure similar to those applied by the respirator used in the

13. Bergmann, E.: Deutsche Ztschr. f. Chir. **243**:761, 1934.

14. Calvé, J.: Brit. M. J. **2**:983, 1934.

15. Herrmann, L. G., and Reid, M. R.: Passive Vascular Exercises; Treatment of Peripheral Obliterative Arterial Diseases by Rhythmic Alteration of Environmental Pressure. Arch. Surg. **29**:697 (Nov.) 1934.

treatment of infantile paralysis. The authors reported that they had used the machine in 51 cases of organic obliterative arterial disease, and they expressed the belief that the device hastened the establishment of collateral circulation to a more normal state, as evidenced by increase in the temperature of the skin. In 86 per cent of their cases improvement was noted; in 14 per cent, no improvement occurred.

*The Digital Vascular System.*—Popoff<sup>16</sup> gave a well illustrated review of the digital vascular system in normal and in pathologic states. He described the specialized arteriovenous anastomosis (glomus) which regulates the local temperature and flow of blood and assists in regulating the temperature of the body. He stated that the improper development or the absence of this glomic system is probably the cause of many thermic and trophic disturbances. No glomus is found in supernumerary digits. These anastomotic units atrophy in old age. In cases of arteriosclerotic gangrene changes in the glomus are due primarily to hyaline degeneration in the afferent artery of the glomus. In cases of diabetic gangrene the intima of the Sucquet-Hoyer canal and that of the preglomerular arterioles are the first to show primary degenerative changes. In cases of thrombo-angiitis obliterans the glomic system appears to be free from primary specific changes. The trophic changes in thrombo-angiitis obliterans were attributed by the author to abnormal anastomoses between arteries and veins. Two types of abnormal anastomoses were observed: a lateral type and a terminal type. Popoff stated that consideration of the glomic system is important in interpreting the symptoms and findings in circulatory disturbances occurring in the hand.

#### NEOPLASMS

*Tumors of the Tendon Sheaths, Joints and Bursae.*—After reviewing the embryologic development of articular structures Geschickter and Lewis<sup>17</sup> classified neoplasms arising from these structures. The common neoplasms of the tendon sheaths were benign osteochondromas and ganglion and giant cell tumors, all of which showed a relationship to hemangioma and lymphangioma. Tumors of the tendon proper and sarcoma were rare. Chondrosarcoma at or near the insertion of tendon into bone and fibrosarcoma of the tendon sheath were described. The most frequent neoplasms of joints were benign osteochondromas or chondromas involving the synovial membrane diffusely (osteochondromatosis) and giving rise to multiple loose bodies. The authors stated that cysts and cartilaginous free bodies of questionable neoplastic nature

16. Popoff, W.: Digital Vascular System, with Reference to State of Glomus in Inflammation, Arteriosclerotic Gangrene, Diabetic Gangrene, Thrombo-Angiitis Obliterans and Supernumerary Digits in Man, Arch. Path. 18:295 (Sept.) 1934.

17. Geschickter, C. F., and Lewis, D.: Am. J. Cancer 22:96, 1934.

may arise from the articular cartilages. Xanthomatous giant cell tumors occurred in the synovial membrane, occasionally invading the articular cartilage and invading bone. They apparently arose in mesenchymal condensations at the primordium of the sesamoid bones and resembled similar tumors within the tendon sheaths. Fibromas, fibrosarcomas and lipomas were described. Bursal tumors were said to be rare. Only 30 cases could be collected from the literature and the records of the Johns Hopkins Hospital laboratory. Benign and malignant chondromatous lesions and spindle cell sarcoma predominated. The prepatellar bursae were most often affected.

*Biologic Relationship of Tumors of the Tendon Sheath to Tumors of the Joints and Bursae.*—Morton<sup>18</sup> in a review of the histologic characteristics of these lesions called attention to the fact that these various tumors of the tendon sheaths are closely related to the tumors of joints and bursae and that the basic cell of all these tumors is the synovial cell, which is a modified mesenchymal cell with the ability to revert in the direction of the fibroblast or to produce cartilage and bone. He therefore gave the following classifications of benign tumors of the tendon sheaths, bursae, joint capsules and joint linings:

Tumors of the Tendon Sheaths	Tumors of the Joints and Bursae
Synovioblastoma "ganglion"	Synovioblastoma
Fibroma	Fibroma
Chondroma or osteochondroma	Intra-articular, Extra-articular chondromatosis
Giant cell xanthoma	Giant cell synovial membrane tumors
Angioma	Angioma
Hemangioma	Hemangioma
Lymphangioma	Lymphangioma
Lipoma	Lipoma

In the group of malignant tumors Morton placed the synovigenic sarcomas. These contain many of the elements derived from the synovial membranes or from the tissues in apposition to them. The cases reported are as yet too few to permit classification of the tumors into anatomic types. Metastatic involvement of tendons, bursae or joints practically never occurred.

*Bony Metastases from Malignant Conditions of the Prostate.*—The following types of bony metastases from primary carcinoma of the prostate were presented by Olin:<sup>19</sup>

1. Osteoplastic: In cases of osteoplastic metastases the roentgenogram showed areas of bone much more dense than the surrounding

18. Morton, J. J.: Surg., Gynec. & Obst. 59:441, 1934.

19. Olin, H.: Illinois M. J. 66:388, 1934.

normal bone. Examination revealed the metastatic areas to be firm and white without destruction of bone. Histologically, large, new trabeculae were seen surrounding nests of columnar cell carcinoma as originally seen in the primary tumor in which, according to Stewart, the stroma usually predominates.

2. Osteoclastic: Osteoclastic metastases destroyed normal bone and produced areas of rarefaction. Olin referred to the theory of Stewart that in this type of neoplasm the primary tumor shows a preponderance of medullary cell growth. A combination of osteoplastic and osteoclastic types may appear. Also, the solitary nodular type of metastases may occur in such numbers as to "pepper" the entire bony architecture. Besides the types mentioned, invasion of lymphatic glands and viscera may occur, though they are rarely observed, without bony metastases.

*Endothelial Myeloma; Analysis of Cases.*—The important features of endothelial myeloma (Ewing's tumor) were presented by Campbell.<sup>20</sup> The data were based on a careful study of 23 cases, 17 of which were registered with the Registry of Bone Sarcoma of the American College of Surgeons. The work of Geschickter and Copeland<sup>21</sup> was referred to frequently, as Campbell compared his observations with those of these authors. He concluded that the nature of the tumor had as yet not been absolutely established, but the structure, he stated, "may approach that of angio-endothelioma, or myeloma." The long bones most frequently affected were the tibia, femur, humerus and fibula, and among the flat bones the pelvis, scapula, clavicle and ribs were most commonly involved. Local metastasis to glands and to the skull were not uncommon. The clinical picture frequently resembled that of acute osteomyelitis or of the sclerosing osteomyelitis of Garré. Four of the 17 patients had been operated on with a diagnosis of osteomyelitis before the true nature of the disease was known.

*Angioma of the Spine.*—Liève<sup>22</sup> summarized 26 cases of angioma of the spine reported in the literature or observed personally. In none of the cases was more than one vertebra involved. The symptoms were those of compression of the cord or nerve roots; local symptoms, though sometimes present, were of a minor nature. Only by means of roentgenograms could a definite diagnosis be made. Compression of the vertebral body was present in only 2 cases. There were irregular areas of diminished density giving a porous, spongy appearance, the

20. Campbell, W. C.: *J. Bone & Joint Surg.* **16**:761, 1934.

21. Geschickter, C. F., and Copeland, M. M.: Multiple Myeloma, *Arch. Surg.* **16**:807 (April) 1928; Ewing's Sarcoma: Small Round Cell Sarcoma of Bone, *ibid.* **20**:246 (Feb.) 1930.

22. Liève, J. A.: *Presse méd.* **42**:1571, 1934.

general density of the whole mass being greater than that of normal bone. The shape of the involved vertebra varied greatly, ranging from a nearly normal size to a markedly increased size and irregularity of contour. Radiotherapy preceded, when necessary by laminectomy gave the best results in ameliorating symptoms and prolonging life.

#### MYOPATHIES

*Glycine Therapy for Various Myopathies.*—Tripoli and his co-workers<sup>23</sup> studied the effect of the use of glycine on eleven different pathologic myopathies, including myasthenia gravis, progressive muscular dystrophy, progressive pseudohypertrophic muscular dystrophy, muscular wasting from disuse, progressive spinal muscular atrophy, subacute and chronic poliomyelitis, multiple sclerosis, amyotrophic lateral sclerosis, muscular paralysis from jamaica ginger poisoning, muscular paralysis from peripheral nerve section and Friedreich's ataxia. They found that primary myopathies and myasthenia gravis showed distinct clinical improvement under treatment with glycine and that the inclusion of this amino-acid in the diet increased the appetite and body weight in most of the patients with muscular dystrophy and muscular atrophy.

[ED. NOTE.—The authors have included eleven separate types of myopathies and reported the results of treatment in 43 patients. It seems that the number of patients in each group is too small to allow accurate statements of the results. Several of the editors have used glycine therapy for pseudohypertrophic muscular dystrophy without any striking improvement.]

*Chemical Examination of the Muscles in Myasthenia Gravis, Pseudohypertrophic Muscular Dystrophy and Myotonia.*—Nevin<sup>24</sup> investigated the phosphorus-holding compounds of muscle in cases of myasthenia gravis, pseudohypertrophic muscular dystrophy and myotonia. He found that the content was normal in patients with myasthenia gravis and concluded that further study of the etiology of this disease should be devoted to an investigation of the excitatory transmission at the neuromuscular junction rather than along metabolic lines. He considered that alterations from the normal observed in muscles of patients with hypertrophic muscular dystrophy and myotonia are due to the degeneration of the muscles and cannot be regarded as a cause of the degeneration. The possible explanations of reported beneficial results following glycine therapy were discussed.

23. Tripoli, C. J.; McCord, W. M., and Beard, H. H.: *Muscular Dystrophy, Muscular Atrophy, Myasthenia Gravis and Strabismus; Clinical and Biochemical Studies of Amino Acid Therapy*, J. A. M. A. **103**:1595 (Nov. 24) 1934.

24. Nevin, S.: *Brain* **57**:239. 1934.

*Investigations of the Myopathies.*—Paulian<sup>25</sup> examined muscle tissue from 14 patients with primary myopathy. He purposely did not try to classify his cases into different types as he believed that such classifications did not constitute clinical entities and that the so-called pseudo-hypertrophic juvenile, scapulohumeral and other types all have common characteristics and probably a common origin. His conclusions were that the grouping of the myofibrils in a spiral system and the presence of the nucleus of the muscle in the axis of the fibers suggest embryologic muscular tissue. The presence of histopathologic characteristics of embryonic muscle led him to believe that the myopathies are due to some undetermined change in the growth-regulating mechanism, either primary in the germ plasma or secondary in the endocrine system, which causes a retardation of normal muscle development and a degeneration toward the original embryologic tissue.

#### INJURIES ABOUT JOINTS

*Osteochondritis Dissecans.*—Hellström and Ostling<sup>26</sup> reviewed 73 cases of osteochondritis dissecans. In 46 of these the lesion was in the joint of the knee, in 24, in that of the elbow joint; in 1 each, in the first metacarpal and the first metatarsal region, and in 1, in the astragalus. Most of the patients were engaged in heavy labor. Twenty-four per cent of the lesions in the knee and 4 per cent of the lesions in the elbow were in women. In 4 cases the lesions in the knee were bilateral. Both elbows were involved in 2 cases. Three fourths of the cases were in young adults. The usual symptoms were pain on motion and limitation of motion. "Locking" was observed without a foreign body being present. Occasionally capsular thickening or hydrarthrosis was observed. Only 2 patients were free from symptoms when the lesion was discovered; 1 of these had a lesion in the knee, and 1, a lesion in the elbow. The history and the roentgenogram showing the articular structure were of most help in making the differential diagnosis. It was observed that loose bodies shed from the articular surface in some cases increased and in others, decreased in size, and in some became reattached to the articular surfaces or the capsule. The authors concluded that most cases are the result of trauma but that constitutional and hereditary factors predisposed to this disease. Treatment should be expectant for patients who exhibited no symptoms, and the authors advised that in such patients the course of the disease should be closely followed by roentgenograms. They stated that free bodies and necrotic pieces of cartilage which were partially loose should be immediately removed, provided they could be removed without trauma

25. Paulian, D.: Presse méd. 42:2067, 1934.

26. Hellström, J., and Ostling, K.: Acta chir. Scandinav. 75:273, 1934.

to surrounding structures. Arthritis deformans developed later in most of the cases.

*Loose Bodies in the Elbow Joint.*—Kamniker<sup>27</sup> reported 6 cases in which free bodies in the joint limited either flexion or extension. In most instances a traumatic origin from the external condyle was adduced. Indirect trauma pulled off pieces of cartilage, the author believed. Surgical removal was advised.

*Injuries to Muscle and Tendon in the Shoulder Region.*—Soto-Hall and Haldeman<sup>28</sup> reviewed 86 cases of injuries to muscle and tendon, 40 per cent of which occurred in the shoulder. The cases were classified as follows: tear of the supraspinatus tendon, 13; rupture of the long head of the biceps tendon, 6; rupture of the short head of the biceps tendon, 2; slipping of the long head of the biceps tendon, 2; rupture of the triceps tendon, 2; injury to the rhomboidens major muscle, 6; injury to the latissimus dorsi muscle, 2, and injury to the trapezius muscle, 1. The authors stated that when an acute case of tear of the supraspinatus is suspected the inhibition of function in that tendon as a result of pain in the bursa may be ruled out by injecting 8 or 10 cc. of procaine hydrochloride into the bursa. If the tendon is not affected a full range of abduction of the shoulder becomes possible within a few minutes. The technic of injecting the drug into the bursa was as follows: The needle was directed toward the upper border of the great tuberosity until it struck bone. It was then withdrawn  $\frac{1}{8}$  inch (0.32 cm.), and an attempt to withdraw fluid within the bursa was made; after this the procaine hydrochloride was injected.

*Pathologic Characteristics and Treatment of Sprains.*—The functional importance of the areolar tissue filling up the interspaces between the structures surrounding joints was emphasized by Smart<sup>29</sup> in a study of sprains. After sustaining an injury this tissue became edematous, and if the edema was not dispelled a stiffness of the joint resulted. The keynote of recovery after injury to a joint was taken to be the rate and completeness of the absorption of the effusion. The value of electrical stimulation of the muscles controlling the movement of the joint was pointed out.

#### MISCELLANEOUS

*Tetanus Treated with Curare.*—Two cases of tetanus in which curare was used were reported by Cole.<sup>30</sup> In both cases the curare

27. Kamniker, K. D.: Deutsche Ztschr. f. Chir. **243**:464, 1934.

28. Soto-Hall, R., and Haldeman, K. O.: California & West. Med. **41**:318, 1934.

29. Smart, M.: Brit. M. J. **2**:673, 1934.

30. Cole, L.: Lancet **2**:475, 1934.

seemed to reduce the continuous rigidity of the muscles of the limbs, abdomen and jaw and to lessen the reflex excitability and the frequency and duration of the spasms. The results were encouraging, but the authors stated that more knowledge regarding the drug and the particular actions of its various alkaloids is required.

*Caisson Disease with Pain in the Hip Joints.*—After describing the generally known aspect of caisson disease and the incidence of "bends" in his group of patients Christ<sup>31</sup> described what appears to be a new syndrome. So-called "arthritis" has been mentioned by observers before. In four of his patients Christ found a clinical picture of limp, local tenderness in the hip and slight limitation of motion of the hip joint. These patients complained of mild pain. Roentgenograms revealed striking changes in the heads of the femurs of these workers, who were in the third decade of life. Local areas of absorption were present in the cancellous bone of the head of the femur and were followed by a slight secondary arthritic change, but the changes in the head of the femur were doubtless primary. The lesions occurred in workers who had suffered no direct traumas but had worked for years in caissons. Christ expressed the belief that the lesion was probably due to often repeated numerous gas emboli which had eventually damaged the blood supply to local areas in the head of the femur.

*Arthralgia and Myalgia Due to the Use of Barbiturates.*—Castin and Gardeen<sup>32</sup> reported 6 cases of disorders in the joints due to the use of various forms of the barbiturates. Symptoms were almost entirely subjective, the only objective finding being a slight atrophy of the deltoid muscle in one case. The symptoms, which consisted of pain in the joints and adjacent groups of muscles, were usually limited to a single articulation. The manifestations in the joints came on in the latter part of life. Often the patients had had symptoms of poisoning, such as cutaneous eruptions, digestive disturbances, etc., repeatedly in earlier life, and not until the fourth or fifth decade did symptoms in the joints appear. Roentgen and physical examination gave negative results.

*Meniscal Cysts.*—In a review of the literature on meniscal cysts, Nicole<sup>33</sup> emphasized the comparative frequency of this lesion. He stated that one cannot always distinguish between the parameniscal and intrameniscal cysts, as Mandl had maintained. The etiology is still a matter of dispute. Nicole stated that a traumatic origin is probably unlikely and that possibly trauma is never the primary cause of meniscal cysts. Taffee's belief that these cysts are truly neoplasms of

31. Christ, A. D.: *Deutsche Ztschr. f. Chir.* **243**:132, 1934.

32. Castin, P., and Gardeen, P.: *Presse méd.* **42**:1536, 1934.

33. Nicole, R.: *Deutsche Ztschr. f. Chir.* **243**:147, 1934.



the joints arising from synovial cells was said to be of interest in this connection. Nicole expressed the belief that constitutional factors may be involved since the lesion nearly always occurs in the second and third decades of life.

[ED. NOTE.—Meniscal cysts probably arise from several different causes. Some of them are congenital malformations. One of the editors has observed such cysts in the intra-articular fibrocartilage at autopsy on 2 premature infants.]

*The Symphysis Pubis in Women.*—Barnes<sup>34</sup> reviewed the anatomy of the symphysis pubis. It was estimated that a force of from 400 to 2,600 pounds (180 to 1,180 Kg.) was necessary to rupture the normal symphysis pubis. Rupture occurred once in from 5,000 to 30,000 deliveries. During pregnancy the relaxation of the symphysis was less than 1 cm. Twenty-six per cent of the multiparas showed widening of the symphysis pubis amounting to 8 mm. or more. Fairly prompt return to normal, the process taking one month, was observed in these cases. Barnes stated that after trauma sustained in childbirth the intra-articular disk of the symphysis may show degenerative changes, and the ligaments, fatty infiltration. According to Barnes, there are many causes of pelvic relaxation and endocrine influences play a major rôle in bringing about such relaxation.

[ED. NOTE.—The pelvic articulations in pregnancy<sup>35</sup> have been discussed in the fifty-third and fifty-fifth reports of progress in orthopedic surgery.<sup>36</sup>]

#### ORTHOPEDIC OPERATIONS

*Tuberculosis of the Hip Joint Treated by Fusion Operation.*—In a review of the end-results in 170 consecutive unselected cases in which arthrodesis was performed during the period from 1923 to 1931 according to the technic devised by Dr. Hibbs and used in his clinic, Hallock and Toumey<sup>37</sup> reported the following results: 7 patients (4.11 per cent) died within the first postoperative year. Of the 163 patients who survived for more than a year, 68.7 per cent obtained fusion by the first operation. Forty-one patients underwent a second operation; in 26 instances (66⅔ per cent) it was successful. Hallock and Toumey

34. Barnes, J. M.: *Am. J. Roentgenol.* **32**:333, 1934.

35. Boland, B. F.: *New England J. Med.* **208**:431, 1933. Abramson, D.; Roberts, S. M., and Wilson, P. D.: *Surg., Gynec. & Obst.* **58**:593, 1934.

36. Kuhns, John G., and others: *Fifty-Third Report of Progress in Orthopedic Surgery*, *Arch. Surg.* **28**:1176 (June) 1934; *Fifty-Fifth Report of Progress in Orthopedic Surgery*, *ibid.* **29**:1076 (Dec.) 1934.

37. Hallock, H., and Toumey, J. W., Jr.: *Hip Joint Tuberculosis Treated by Fusion Operation; End-Result Study of 170 Unselected Cases*, *J. A. M. A.* **103**:1836 (Dec. 15) 1934.

considered the factors hindering fusion to be faulty operative technic and faulty immobilization in plaster after operation.

[ED. NOTE.—The article by Hallock and Toumey represents an important study of end-results as their data are based on the largest series of patients with tuberculosis of the hip treated by fusion yet reported. Their observations definitely tend to support the present consensus that the best end-result of treatment of tuberculosis of the hip is a hip fused in good weight-bearing position.]

*Disabilities of the Hand Resulting from Loss of Function of the Joint.*—In a carefully written article, the troublesome question of loss of function in the hand from limitation of motion in finger joints was considered, and the various procedures available were discussed by Koch.<sup>38</sup> In cases in which the function was only partially limited and the condition had not been of too long standing the best results were obtained by the use of splints and application of well directed physical therapy carried out daily for prolonged periods. Elastic traction with the banjo splint was considered to be of real value if carefully used. Manipulation of the joints under anesthesia usually resulted in limiting rather than improving the power of motion, as the hemorrhage and trauma to the soft tissue resulted in further scarring unless active motion could be begun immediately after the manipulation and carried out faithfully. This was often impossible because of the discomfort immediately following manipulation. Koch called attention to the importance of the collateral ligaments of the finger joints and stated that capsulorrhaphy as advocated by Shaw has been of real value in certain instances. Intra-articular operations, such as arthroplasty, were usually of little value in the small joints of the fingers, as the pathologic changes involved not only the joints but the tendons and other soft tissues. Koch stated that in certain instances arthroplasty of the wrist has been of real value.

*Muscular Incisions and Neurotization of Muscles.*—Seeman<sup>39</sup> presented his findings concerning neurotization after splitting of the muscle or incisions which divided the nerve supply to the entire muscle or to part of it. He showed that in experimental animals the longitudinal abdominal incision dividing the nerves to the rectus abdominis muscles resulted in permanent paralysis and that in animals with such an incision fat eventually replaced the muscle fibers. Three years after operation no evidence of nerve regeneration was present. Histologic study of portions of human muscle devoid of nerve supply as the result of muscular incisions always showed a high degree of atrophy with

38. Koch, S. L.: Disability of Hand Resulting from Loss of Joint Function. J. A. M. A. 104:30 (Jan. 5) 1935.

39. Seeman, H. V.: Deutsche Ztschr. f. Chir. 243:274, 1934.

hyaline degeneration. Replacement of muscle bundles by fat and connective tissue had occurred in places. These principles so often forgotten required restatement, Seeman insisted. He pointed as an example to the muscle-splitting, longitudinal incision into the deltoid muscle: In this muscle the nerves and vessels run at right angles to the muscle fibers, and if the anterior muscle fibers are not to be paralyzed, the incision must be changed. He urged the general use of the incision between the pectoralis major and the deltoid muscle with freeing of the deltoid muscle from the clavicle to enlarge the approach.

[ED. NOTE.—The frequency of paralysis of the anterior portion of the deltoid muscle in the wake of the increasing use of the longitudinal incision splitting the deltoid muscle is of considerable moment. One of us has seen 3 such cases within the past two months; in 2 the incision was made for approaches to the supraspinatus muscle.

*Volkman's Paralysis Treated by Arteriotomy.*—Mathieu and his co-workers<sup>40</sup> described a case of Volkman's paralysis seen three months after onset. The patient had had a supracondylar fracture of the humerus treated by manipulation and application of plaster. Six days later the plaster had been removed because of pain and swelling, and a pressure sore was found in the fold of the elbow. Five weeks later signs of Volkman's contracture were noted. When seen by the authors the patient presented the typical picture of Volkman's paralysis with trophic ulcers of the fingers. There was a diminution of sensation but no true anesthesia. Operation was performed, and the brachial artery was found to be obliterated at the elbow joint. Two centimeters of the obliterated portion was resected. After operation the atrophic ulcers of the fingers healed, and four months later the fingers and wrist could be extended almost completely. The authors attributed this improvement to the periarterial sympathectomy that took place when the section of artery was removed. Accordingly they recommended that in early stages not only fasciotomy to release hematomas in the forearm but also sympathectomy of the brachial artery be performed if that vessel is intact, or resection, if it is injured. They stated that in late stages sympathectomy should also be performed either as a means by itself or else as a preliminary to other surgical or conservative treatment of the contractures.

#### FRACTURES AND DISLOCATIONS

*Healing of Fractures of the Neck of the Femur After Osteosynthesis with a Stainless Steel Nail.*—Palmer<sup>41</sup> reported the observations at

40. Mathieu, P.; Pedovani, P.; Setille, R., and Norman, P.: Presse méd. **42**: 1819, 1934.

41. Palmer, I.: Acta chir. Scandinav. **75**:416, 1934.

autopsy on a patient aged 70 who died twelve weeks after sustaining a fracture of the neck of the femur which had been immediately nailed with a stainless steel nail. The causes of death were enteritis and bronchitis. In macroscopic and microscopic study of the site of fracture no harmful effects of the nail were seen in the living bone about the nail. There was partial revascularization of the proximal fragment of the femur from the capsule and periosteum. Most of this fragment showed osseous necrosis. Palmer expressed the belief that this form of treatment did not prevent resorptive processes, as shown by the changes in shape and size of the proximal fragment, and that there was risk of displacement. It was necessary to support the hip while healing was taking place.

*Report of 631 Fractures of the Neck of the Femur.*—Henderson <sup>42</sup> reviewed 631 cases of fracture of the neck of the femur. He tabulated the frequency of union after various surgical procedures for 176 fractures. Manipulation by the Whitman method was successful in 65 per cent of the patients with recent fractures and in 50 per cent of those seen three weeks or more after the original injury. Grafting with a fibular graft driven through the neck of the femur resulted in union in 70 per cent of the patients thus treated. This method proved worthy when tried up to three years after the time of fracture. Beef-bone screws or pegs were used when the operation was performed less than six weeks after the injury, and bony union resulted in 75 per cent of the cases. The Whitman reconstruction operation gave excellent results in 31, and good results in 36, per cent of the cases. The Brackett type of operation was performed in five cases, and the result was satisfactory in each case.

*Fractures of the Head of the Tibia.*—Becker <sup>43</sup> found that over 70 per cent of a group of fractures of the head of the tibia involved the knee joint. The most common varieties were lateral monocondylar, bicondylar and infracondylar fractures and fracture of the eminentia intercondyloides. He emphasized the egg-shell compression of the surfaces of the joint. The compression, impression and egg-shell fractures were often accompanied by severe meniscal injuries. Becker insisted on exact reposition of the surfaces of the joint. If closed reduction was unsuccessful, he performed an open operation, exposing the joint and removing the meniscus if necessary. He lifted the depressed fragments into place and supported the depressed condyle with a tibial graft if necessary, or held the fragments in place with an ivory peg. Weight bearing was deferred until roentgenograms indicated that the danger of

42. Henderson, M. S.: *South. M. J.* 27:1032, 1934.

43. Becker, F.: *Deutsche Ztschr. f. Chir.* 243:189, 1934.

recompression seemed past. Mild arthritic changes, mild lateral instability and some limitation of motion were the usual sequelae of the more severe fractures.

*Fractures of the Lateral Condyle of the Tibia.*—In an analysis of fractures of the condyle of the tibia treated at the Cook County Hospital, Cubbins and his associates<sup>44</sup> reviewed the results of the treatment of 125 fractures of the lateral condyle of the tibia occurring in the past six years. In most cases an attempt was made to secure reposition by molding the fragments and retaining them in a plaster cast. In 50 cases open operation was resorted to with elevation of the depressed fragment and maintenance of its position by the use either of bone chips or of a steel screw with a wooden thread. Cubbins divided these fractures into five types and discussed the method of treatment for each of the various types. He stated that the results have been excellent. There were no severe infections. In one case a screw had to be removed. In no case did ankylosis develop. In every case there was a certain amount of genu valgum, but with more perfect reduction. The amount of knock-knee has been less than in the cases occurring early in the series.

*Fractures of the Talus.*—Gibson and Inkster<sup>45</sup> studied the mechanism accompanying fractures of the astragalus on the cadaver. It was found that strong dorsiflexion produced eversion of the heel; this was accompanied by rupture of the posterior astragalotibial and posterior tibio calcaneal fibers of the deltoid ligament and of the medial fibers of the interosseous (astragalocalcaneal) ligament, successively. On a fresh specimen a similar manipulation caused the astragalus to appear between the stretched tendons of the flexor longus hallucis on one side, and the tendons of flexor longus digitorum and tibialis posterior on the other. The tendo Achillis assumed a position lateral to the midline. The mechanism of fracture without dislocation was thought to be produced by forced dorsiflexion beyond normal limits with the line of strain passing through the metatarsal shafts and the cuneiform and navicular bones to the head of the astragalus, and it was believed that any part of this line may give way. If the force continues without any of these parts giving way, the tibia, at its anterior joint line, acts as an apex of a wedge fracturing the neck and pushes the body backward sometimes through the "buttonhole" formed by the flexor tendons. The prognosis was generally regarded as bad, with convalescence requiring many months, and Gibson and Inkster stated that according to some writers

44. Cubbins, W. R.; Conley, A. H.; Callahan, J. J., and Scuderi, C. S.: Surg., Gynec. & Obst. **59**:461, 1934.

45. Gibson, A., and Inkster, R. G.: Canad. M. A. J. **31**:357, 1934.

recovery is never complete. Treatment varies with each case. The authors stated that crushing of the anterior part of the bone can be corrected by manual remodeling, followed by rest in splints, and later by the use of an iron stabilizing apparatus with a T strap. When the body of the bone is crushed a subastragalar arthrodesis may be required to bring about alinement of the foot and leg. When the posterior fragment is displaced backward, reposition of the fragments (provided the blood supply is adequate) and partial or total astragalectomy are the methods available. The authors expressed the belief that partial astragalectomy is unsatisfactory. Case histories of 3 patients who had sustained injury to the astragalus without displacement, and of 3 who had sustained fractures with displacement, of the posterior fragment were given.

*Study of End-Results of Fractures of the Shaft of the Humerus.*—Rogers<sup>46</sup> analyzed the end-results of 82 fractures of the shaft of the humerus treated at the Massachusetts General Hospital between 1925 and 1931; fractures through the surgical neck, supracondylar and pathologic fractures were excluded. Satisfactory results were obtained in 80 per cent of the cases; in 20 per cent the results were relatively unsatisfactory. In the groups in which the patients were confined to bed better end-results were obtained than in groups in which the patients were ambulatory. Rogers concluded that when fractures of the shaft of the humerus are treated intelligently by any suitable method, the end-results are excellent. Generally, transverse fractures should be reduced by manipulation (closed or open) and held by fixation (external or internal). Oblique fractures should be reduced and held by constant traction. And comminuted fractures should be treated by the simplest method suited to the individual case. Constant traction was found to be dangerous. (The device most commonly used was a Thomas arm splint or a Blake suspension with the arm in abduction, the elbow at a right angle and the forearm suspended vertically in transverse or short oblique fractures, especially in the lower and middle thirds.) Traction with the patient in bed (with a Thomas arm splint or a Blake suspension) was always more effective than that with the patient ambulatory (the latter traction may be applied by means of a Jones humeral splint). Open reduction was found necessary only in cases in which nonunion and failure to accomplish satisfactory reduction by closed methods were anticipated. Bone plating alone after bone repair had subsided was found not to bring about secondary union, but it brought about such union in fresh fractures or in those in which bone grafts were used. Nonunion was frequently found in a transverse and short oblique fracture in the middle and lower thirds of the humerus when there had

46. Rogers, H.: Surg., Gynec. & Obst. 59:934, 1934.

been no contact between the ends of the bone during the period of active repair, which was usually considered to last two weeks. Injury to the radial nerve rarely resulted in permanent disability if a cock-up splint was worn and physical therapy was given to the extensor groups of muscles.

*Epiphysiolysis of the Proximal End of the Radius.*—Von Oppolzer<sup>47</sup> attempted closed reduction of fractures of the head of the radius. Eight cases were recounted, successful reposition resulting in each. The maneuver used with the patient under anesthesia may be briefly described as follows: The elbow was extended with the forearm supinated. The elbow was bent into a varus position over the operator's knee, and traction was made on the forearm, increasing the space between the neck of the radius and the external condyle. Then the dislocated head was pushed and manipulated with the thumb, mostly from behind, while the forearm was slowly flexed or pronated. Most of the reductions occurred during the pronation. A nonpadded plaster splint was worn for three weeks.

*Treatment of Fractures of the Carpal Scaphoid.*—For treatment of delayed nonunion of the carpal scaphoid, Soto-Hall and Haldeman<sup>48</sup> recommended that the bone be exposed through a dorsoradial incision and drilled across the line of fracture. Subsequently the fractures were treated as were fresh fractures of the scaphoid, i. e., by immobilization of the thumb and hand in plaster at from 30 to 40 degrees of dorsal flexion and complete radial deviation for from seven to nine weeks. Of 7 cases of delayed union, 5 ended in union after this procedure. Of 16 fractures of the scaphoid 75 per cent resulted in union after immobilization in plaster in the position described. In cases in which there were nonunion and marked deformity total excision of the bone followed by immobilization in plaster in extreme ulnar deviation for from five to six weeks was recommended.

#### RESEARCH

*Cause of Death in Cases of Fat Embolism.*—Rückert<sup>49</sup> stated that, aside from direct cerebral and cardiac lesions, death of patients with fat embolism is due chiefly to renal lesions. In fact, retention uremia experimentally induced is much like cerebral fat embolism in its clinical aspects. He stated that the literature contains conflicting reports on the alterations of the nonprotein nitrogen after intravenous injection of fat into the blood stream. He therefore gave injections to a series of 10 rabbits and 3 dogs and found that small doses of fat given by slow

47. von Oppolzer, R. R.: Deutsche Ztschr. f. Chir. **243**:427, 1934.

48. Soto-Hall, R., and Haldeman, K. O.: J. Bone & Joint Surg. **16**:822, 1934.

49. Rückert, W.: Deutsche Ztschr. f. Chir. **243**:537, 1934.

intravenous injection raised the nonprotein nitrogen moderately. Large intravenous doses (5 cc.) administered rapidly raised the nonprotein nitrogen markedly and in three days led to death with the picture of uremia and cerebral fat embolism. Fat from bone marrow and petrolatum acted similarly. If small doses (from 1 to 2 cc.) were injected directly into the renal arterial supply of a dog the nonprotein nitrogen rose, and if 4 cc. was used the figures rose to fatal levels. Fat injected into the abdominal aorta of a rabbit in doses of 2 cc. caused a rise of 352 mg. of nonprotein nitrogen followed by death of the animal.

*Infection in Cases of Avitaminosis, with Special Reference to the Occurrence of Acute Osteomyelitis.*—Attempts were made by Takahashi<sup>50</sup> to study groups of animals fed on diets lacking the vitamins, to determine the sites of localization of intravenously injected staphylococci. The animals which received food deficient in vitamin A showed a diminished resistance as compared to controls, but exhibited no particular involvement of the muscles. In those which received food lacking in vitamin C metaphyseal lesions in bones frequently developed, while no such lesions occurred in control animals. Doubtless the circulatory disturbances visible in the metaphyses in the animals not receiving vitamin C predisposed to involvement in these regions.

*Assimilation of Phosphorus from Di-Calcium Phosphate, Tri-Calcium Phosphate, Bone Di-Calcium Phosphate and Cooked Bone Meal.*—Three experiments were carried out by Rottensten and Maynard<sup>51</sup> with rats. The phosphorus intake was kept at a minimum level, and the calcium-phosphorus ratio was held constant in the diets under comparison. In the first experiment the effects of di-calcium phosphate and cooked bone meal were compared, growth and development of bone being used as the criteria. In the second experiment chemically pure di-calcium phosphate, bone di-calcium phosphate and chemically pure tri-calcium phosphate were used. In the third experiment the effects of bone di-calcium phosphate and cooked bone meal were studied on female rats carried from weaning through their first lactation. In all these experiments the usefulness of the supplements was shown by the data for ash content of the bones. In the last experiment it was observed not only that the weight of the young rats receiving the supplement exceeded that of the young of other rats but that in the bones of those rats both the percentage and the amount of ash remained higher than in those of the controls which did not receive supplement; a higher level of inorganic phosphorus was also shown in the blood. There was a slightly increased amount of evidence in favor of a secondary over a

50. Takahashi, R.: Arch. f. klin. Chir. **181**:103, 1934.

51. Rottensten, K. V., and Maynard, L. A.: J. Nutrition **8**:715, 1934.



tertiary phosphate, but the difference was too slight to warrant its use in practice.

*Experimental Infarction of the Femur in Rabbits.*—In an attempt to produce experimental lesions of the upper end of the femur in rabbits, Kistler,<sup>52</sup> using rabbits of various ages, injected a 2 per cent suspension of charcoal into the nutrient arteries supplying the upper end of the femur and observed the changes occurring after the lapse of varying lengths of time. He was able to produce definite infarcts of the metaphysis and to follow the reparative changes and subsequent vascularization. He was of the opinion that production of these nutritional disturbances demonstrated conclusively that the vascular system of the upper end of the femur in rabbits is closed. He also noted pathologic changes in the epiphysis and in the region of the epiphyseal line similar to those found clinically in patients with Legg-Perthes' disease. Nutritional disturbances produced in this way affected the rate of growth as well as the rate of ossification of the femur. Areas of increased density in the infarcts were found to be due to deposition of inorganic calcium salts.

*Fractures of the Neck of the Femur, Dislocations of the Hip and Obscure Vascular Disturbances Producing Aseptic Necrosis of the Head of the Femur.*—In a careful clinical roentgenologic and pathologic study of injury to the upper end of the femur Phemister<sup>53</sup> correlated the pathologic changes which occurred. He found that intracapsular fracture of the neck of the femur by injuring the blood supply resulted in aseptic necrosis of a part or all of the head of the femur and that such occurrences increased the likelihood of nonunion of the fracture. The presence of aseptic necrosis could usually be diagnosed by roentgenograms taken two or three months after injury and was characterized by areas of increased density which represented portions of necrotic bone and by areas of decreased density which represented processes of creeping substitution. According to Phemister, the articular cartilage may also become necrotic and be absorbed or replaced by fibrocartilage or connective tissue. Months or years may be required for completion of the change. He stated that it is important to recognize this process clinically and to protect the softened bone from too great weight bearing during the period of transformation in order to prevent collapse of the normal architecture with resultant deformity and impairment of the functional result. He pointed out the fact that similar changes representing aseptic necrosis occurred in certain instances of slipping of the upper epiphysis of the femur, traumatic dislocation of the hip, the

52. Kistler, G. H.: Sequences of Experimental Infarction of Femur in Rabbits, Arch. Surg. 29:589 (Oct.) 1934.

53. Phemister, D. B.: Surg., Gynec. & Obst. 59:415, 1934.

reduction of congenital dislocations of the hip, and arthroplasty for the mobilization of ankylosed hips. He attributed the changes in these cases to interference with the circulation supplying nutrition to the head of the femur and expressed the belief that this interference also caused the aseptic necrosis seen in cases of Legg-Perthes' disease, but he pointed out that so far no single factor such as trauma, embolism, infection, etc., offered an adequate explanation for the pathologic process seen in these cases.

[ED. NOTE.—This article represents observations and deductions gathered from a large collection of clinical cases and from careful studies of pathologic changes in excellent specimens. It helps to clarify the pathologic picture seen in a variety of conditions and points the way toward a more rational treatment.]

*Studies in Sarcoma of Bones.*—In an effort to stimulate formation of new bone in tumor tissue Brunschwig and Harmon<sup>54</sup> injected calcium in various forms into the tissue of transplanted rat tumors in 37 instances. Viosterol was also given by mouth. In no case, however, was there formation of new bone, which furnished evidence against the hypothesis that bone in osteogenic sarcoma, or its metastasis, is merely the result of a mesoblastic tumor in proximity to a supply of calcium. The experiments also demonstrated that calcium could not produce osteogenic properties in malignant mesoblastic cells if such properties were not already exhibited by these cells.

*Rôle of Bone and Endosteum in Regeneration of Bone.*—In experiments on 6 dogs McGaw and Harbin<sup>55</sup> resected a section of fibula with periosteum and in the defect thus created inserted curettings of bone marrow and endosteum from the opposite tibia. In all the animals there was regeneration of bone, and in from twenty-one to twenty-nine days there was a distinct homogeneous callus. In sixty days a medullary cavity was established, and in all the animals the new bone was well fused to the shaft of the fibula.

*Experimental Regeneration of Bone with Lime Salts and Autogenous Grafts as Sources of Available Calcium.*—Dogs were used in an experimental study by Stewart<sup>56</sup> to verify the findings of Murray.<sup>57</sup> In each instance grafts of boiled bone died when inserted into defects of the radius; furthermore, there was no production of new bone about or within those defects. The only source available for the formation of new bone was from the ends of the radius. When lime salts were implanted in radial defects there was failure of regeneration of the

54. Brunschwig, A., and Harmon, F. H.: *Am. J. Cancer* **22**:342, 1934.

55. McGaw, W. G., and Harbin, M.: *J. Bone & Joint Surg.* **16**:816, 1934.

56. Stewart, W. J.: *Surg., Gynec. & Obst.* **59**:847, 1934.

57. Murray, C. R.: *Ann. Surg.* **93**:463, 1931.

shaft. Small fragmented live grafts similarly used or small chips of bone accidentally left behind at operation consistently showed growth of new bone in large amounts. When traumatized muscle and lime salts were mixed and placed in the radial defect a few areas of calcification were seen, but no regeneration of the shaft occurred. Proliferative arthritis resulted from implantation of lime salts in carpal and tarsal defects, but no new bone was laid down after such implantation.

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## PILONIDAL SINUS

AN EXPLANATION OF ITS EMBRYOLOGIC DEVELOPMENT

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NEW ORLEANS

The term "pilonidal," derived from the Latin *pilus*, meaning hair, and *nidus*, meaning nest, was first applied to sinuses in the sacral region by Hodges<sup>1</sup> in 1880. However, the lesion was in all probability first described by J. W. Warren<sup>1</sup> in 1867. Since the first description of the lesion many terms have been suggested, such as "coccygeal, sacro-coccygeal or sacral sinus, dimple or fistula"; "postanal dimple, fistula or fissure"; "posterior umbilicus"; "postsacral or sequestration dermoid." From clinical usage the term "pilonidal sinus" has supplanted practically all of the other terms. At present the term "pilonidal cyst" or "pilonidal sinus" should be limited to those cysts or sinuses having their origin from the medullary canal, which should not be confused with the simple type of sacral dimple.

The etiology of this interesting anomaly has been most intriguing to the majority of writers describing the sinus, as attested by the numerous and, in some instances, fanciful theories regarding its formation. However, most of the authors agree that this clinical entity is a congenital malformation.

Warren, probably the first to offer a theory concerning the formation of a pilonidal cyst, suggested in 1867 that it is due to a change in growth of the hair follicles in the sacral region. Hodges, in 1880, thought it to be due to invaginations of hairs in the postnatal fold. Mallory,<sup>2</sup> Tourneaux<sup>3</sup> and Oehlecker<sup>4</sup> demonstrated vestiges from this canal that formed cysts and sinuses in the sacral region in the fetus. According to Kuhn,<sup>5</sup> such findings were residua of spina bifida, whereas Tait<sup>6</sup> thought they were residua of the caudal appendage. Féré<sup>5</sup> considered the failure of the two halves of the body to unite responsible

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1. Quoted by Gleen, Frank: Pilonidal Sinus, New England J. Med. **207**: 544, 1932.

2. Mallory, F. B.: Am. J. M. Sc. **103**:269, 1892.

3. Tourneaux and Hermann, quoted by Keibel and Mall.<sup>10</sup>

4. Oehlecker, F.: Sacral Abscesses in Congenital Skin Displacements, Deutsche Ztschr. f. Chir. **197**:262, 1926.

5. Quoted by Couraud.<sup>1</sup>

6. Quoted by Weeder, S. D.: Pilonidal Cyst, Ann. Surg. **98**:385, 1933.

for their formation. Welen Stadt<sup>1</sup> stated that "the spinal cord was the last portion to lose its connection with the skin. Therefore, the sacrum in closing its dorsal aspect pinches off the skin, leaving a fibrous cord which causes the skin to retract as the parts grow out, thus forming a dimple." Mummery<sup>1</sup> believed that the sinus is only an exaggeration of the postnatal dimple and that it is a sequestration dermoid due to inclusion of skin. Bevan<sup>7</sup> suggested that the sinus develops congenitally from a bur of epithelium which has been turned under the integument, and Bookman<sup>6</sup> believed that the sinus occurs as a result of the breaking down of sacro-coccygeal cysts. In 1924 Stone<sup>8</sup> stated that "the sinus developed from a special downgrowth of the epithelium and not from the medullary canal." He was unable at that time to name the etiologic factor responsible for this downgrowth of true skin. However, in 1931, he explained this special downgrowth of true skin by comparing the pilonidal sinus found in man, in its development and formation, to the preen gland that occurs in a great many species of birds. Wharton<sup>9</sup> agreed with Stone and considered the analogy to the preen gland to be an excellent explanation of the development of the pilonidal sinus. Other interesting explanations have been given. However, by reviewing a few of the different theories of the origin of pilonidal cysts, one can see how incomplete the knowledge of their formation and development is at the present time. I believe this wide diversity of opinions regarding the origin, formation and development of pilonidal cysts and sinuses to be responsible for the high incidence of recurrence following attempts at surgical removal. I am convinced that the only way one can satisfactorily determine the origin of pilonidal cysts and draw definite conclusions is by studying the embryologic development of the caudal end of the embryo with special reference to the development of the integument, its appendages and the nervous system. This should be correlated with a clinical study of cases of pilonidal sinus as well as with pathologic and histologic studies, with differential staining of numerous sections, removed from different areas of tissue obtained at operation. The object of this paper is to present evidence (which in the author's opinion is conclusive) deduced by these methods of study to show that the pilonidal sinus results from an anomalous development of the medullary canal, and that the coccygeal dimple results from disturbances in the development of the coccygeal ligament and is not connected with the medullary canal.

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7. Bevan, A. D., quoted by Anderson, J. K.: *Diagnosis and Treatment of Pilonidal Sinus*, Minnesota Med. **14**:421, 1931.

8. Stone, Harvey B.: *Pilonidal Sinus*, Ann. Surg. **79**:410, 1924; **94**:317, 1931.

9. Wharton, D. J.: *Pilonidal Cyst*, U. S. Nav. M. Bull. **30**:350, 1932.

## EMBRYOLOGY OF CAUDAL END OF EMBRYO

The embryologic development of the caudal end of the embryo will now be reviewed, with special attention to the ectoderm, its derivatives and the mesoderm—to the latter only as it applies to the formation of the sacrum, coccyx and coccygeal ligament. I believe that the entire solution of this interesting problem is dependent on an understanding of the developmental anomalies occurring in these germ layers in the caudal anlage of the embryo.

After the formation of the ectoderm and entoderm, the indentation, or primitive streak, occurs. Soon two folds appear on each side of the streak. These ridges are known as the medullary folds and give rise to the medullary groove. While the medullary folds increase in height the medullary groove increases correspondingly in depth. When the medullary folds increase in height they incline toward each other, so that their edges finally come in contact and later fuse. By this process the medullary groove becomes converted into the medullary canal. The mesoderm begins to grow in from the sides between the ectoderm and the entoderm to form the supportive structure of the newly formed neural canal. This medullary canal later becomes the central nervous system by a process of evolution of the primitive cells of the walls of the canal, the canal proper, persisting as the central canal of the spinal cord, widening out in the cephalic end to form the ventricles of the brain. The layer of ectoderm that forms the roof remains attached to the medullary canal by a mass of cells. On the dorsal surface, this mass of cells represents the neural crest. However, as development proceeds the ectoderm is entirely separated from the neural crest, which continues to develop lateral to the medullary canal, giving rise to the spinal ganglions and sympathetic nervous system. (Keibel and Mall,<sup>10</sup> Hardesty<sup>11</sup> and McMurrich<sup>12</sup>). The closure of the medullary groove starts near the future cervical region and spreads in both directions. Therefore, the caudal end closes later than the cephalic. At about this period of development of the embryo special consideration of the caudal end of the medullary canal is advisable. This part of the medullary canal exhibits departures from the uniform development of that part of the canal from which the spinal cord and brain develop. If one examines a sagittal series through an embryo 11 cm. long, it can be seen that the extreme tip of the cord lying in the tail anlage has been closed off from the rest of the medullary canal to form a simple

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10. Keibel, F., and Mall, F. P.: *Human Embryology*, Philadelphia, J. P. Lippincott Company, 1912, vol. 2, p. 57.

11. Hardesty, in Morris: *Human Anatomy*, edited by C. M. Jackson, ed. 5, Philadelphia, P. Blakiston's Son & Company, 1914, pl. 3.

12. McMurrich, J. P.: *The Development of the Human Body*, ed. 4, Philadelphia, P. Blakiston's Son & Company, 1914.

epithelial sac. The lumen of the cord above this point becomes obliterated, and there results a slender strand of nervous tissue which later becomes the *filum terminale*. The epithelial sac becomes the "*vestiges medullaire coccygienne*" of Tourneaux and Hermann.<sup>3</sup> Tourneaux described the development of the sac as follows: "At the beginning of the third month the neural tube still extends to the extreme end of the vertebral column into the tail bud, and its slightly elongated tip is closely united to the deep layers of the skin." The tube may remain patent at its junction with the skin (Mallory<sup>2</sup>). Toward the end of the third month the spinal column, developing faster than the soft parts, draws along that part of the neural canal which is adherent to it, the extreme tip of which remains attached to the skin. As a result of the unequal growth the terminus of the coccygeal portion of the neural canal becomes bent in the form of a loop, the more deeply situated limb of which is attached to the posterior surface of the coccyx (*segment coccygien direct*), while the more superficial limb extends obliquely from a caudal and ventral position to one more dorsal and cranial (*segment coccygien reflecti*). During the course of the fourth month the more deeply situated limb atrophies and disappears, while the more superficial one continues to develop into the fifth month and gives origin to cell cords or cell masses which contain cavities lined either with prismatic or with pavement epithelium. These structures from the sixth month on suffer a progressive atrophy, but it is possible to recognize traces of them up to the time of birth.

According to Mallory,<sup>2</sup> who has examined a number of fetuses from 3 to 4 months old, there is frequently found over the coccyx a canal lined by epithelium. In some instances the canal is connected with the skin; in other instances it is separated from it. This canal may be close to the skin without communicating with it, or it may be situated near the periosteum on the dorsal surface of the coccyx.

According to Oehlecker,<sup>4</sup> one can distinguish in the 12 mm. embryo a vertebral and a nonvertebral tissue, the nonvertebral portion being known as the caudal filament. This filament is a prolongation of the connective tissue of the caudal vertebrae. The caudal vertebrae now begin to grow rapidly, and the overlying skin, being unable to keep pace with the downward progress of the caudal vertebrae, is displaced posteriorly and upward, as is also the tip of the caudal filament or ligament. By the fourth or fifth month the skin which originally covered the tip of the coccyx is drawn upward and now occupies a position over the third or fourth caudal vertebra. At the site of attachment of the caudal ligament to the skin there is a thin, hairless, vascular area which Oehlecker has named the "sacral bald spot" of the embryo. The caudal ligament attached to the skin exerts a certain pull on the skin at the point of attachment, producing a depression of the skin. This

depression is known as the coccygeal dimple. Oehlecker also demonstrated that the caudal vestiges of the medullary canal form epithelial-lined spaces and sinuses located over the upper part of the coccyx or lower part of the sacrum. In this observation he is in agreement with Mallory,<sup>2</sup> Tourneaux and Hermann<sup>3</sup> and Keibel and Mall.<sup>10</sup> Therefore, one can state from the observations of these authors that the formation of these epithelial-lined spaces situated over the sacro-coccygeal region, which may or may not have a communication with the skin, has a definite embryologic basis.

Another observation that has been proved beyond doubt is that these cystic cavities and sinuses in the embryo, as well as the same cysts and sinuses in the adult, are lined with epithelium of the pavement or stratified type. Therefore, a review of the development of the skin and its appendages will explain some of the histologic peculiarities found associated with the epithelial lining of the cysts and sinuses removed by operation from children and adults. The following description is from Maximow.<sup>13</sup>

During the first two months of embryonic life the epidermis is represented by two layers of cells, the external and internal. The internal layer which lies on the mesenchyme consists of cuboidal or cylindrical cells which multiply rapidly. The peripheral layer, the so-called peridermis, consists of thin flat cells which do not multiply independently, but which are constantly formed anew from the elements of the deep layer.

Beginning with the third month, the peripheral cells become cornified in certain places and are transformed into large, thin, thorny scales, without the participation of keratohyalin or eleidin; they are gradually desquamated. The epidermis at this time becomes three-layered and still later stratified. Between the peridermis and the basal layer the interstitial layer appears, at first consisting of separate cells, then of one continuous row of flattened elements, and still later of polyhedral cells which increase in number, and are flattened towards the surface. These cells are connected with one another by intercellular bridges, and are penetrated by tonofibrils located in the ectoplasm.

The first appendage of the skin and probably the most primitive of all the appendages is the hair follicle and hair shaft. In man the hair first appears at the end of the second month in the eyebrows, and on the chin and upper lip. Hair always develops in the same manner. At first in the deep layer of the epidermis a group of closely adjoining cylindrical dividing cells appear. These grow into the underlying connective tissue and produce a gradual elongating, compact, epithelial cylinder. This is the primordium of the hair follicle, the so-called "hair germ." It is rounded and slightly flattened on its end. Connective tissue condenses under the latter very early, and from it the hair papilla forms, and proceeds from below into the epithelial mass of the bulb, which at this time forms a cap for the papilla. The epithelial cells at the surface of the connective tissue papilla represent the matrix of the future hair. The axis of the bulb is not perpendicular to the surface of the skin but is oblique.

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13. Maximow, A. A.: *A Text-Book of Histology*, edited by William Bloom, Philadelphia, W. B. Saunders Company, 1930.



The sebaceous glands develop from the formed hair shafts. The primordium of the sebaceous gland develops from the posterior part of the epithelial sheath of the hair shaft, first by proliferation of the epithelial cells with subsequent outgrowth of these cells into the surrounding connective tissue. The central cells early undergo a fatty transformation, forming the first evidence of the future sebaceous gland. These central cells desquamate and are discharged from the hair shaft on to the surface of the body of the fetus, forming the vernix caseosa.

The last appendage of the epidermis to be formed is the sweat gland, which develops independently of the hairs in the majority of places of the skin. The first primordia of the sweat glands occur during the fifth month of embryonic life, on the soles of the feet, and the palmar surfaces of the fingers. At first they are similar to the primordia of the hair follicle which develops from the same basal layer of epithelium. An epithelial shaft with terminal thickening grows into the underlying connective tissue, but unlike the hairs, the connective tissue here does not condense about the epithelium. The shaft gradually elongates, becomes cylindrical, and its lower end curls into the form of a ball. Beginning with the seventh month an irregular lumen forms in this lower portion which constitutes the secretory part; along the course of the future excretory duct another lumen develops which later enters with the secretory part. The entire apparatus of the sweat gland, secretory part and the excretory part, start their development about the fifth month and are complete about the seventh month of embryonic life.

#### PREDICTABLE ABNORMAL DEVELOPMENTS

From the foregoing description of the embryologic development of the caudal end of the neural canal in the fetus, one can predict that certain formations occur. Of importance in explaining these formations is a knowledge of the conversion of the caudal end of the neural canal into the filum terminale, the development of the sacral and coccygeal vertebrae, the caudal ligament, and its peculiar attachment to the skin, the development of the integument or covering of the body as well as the development of the several appendages of this integument. These formations occur with such regularity that any deviation from normal may result in the persistence of these formations which become abnormal in their growth and development. This is in conformity with the law of Rienhoff,<sup>14</sup> which states: "There is in the life cycle of a cell or tissue, which is differentiating or growing, a period in which the cell is very sensitive to its environment, and any injury of it at this stage will result in the abnormal growth and development of that cell or structure."

The embryologic structures or formations that can be predicted with certainty are as follows:

(a) In the closure of the caudal end of the neural canal, that part of the canal between the coccygeal vertebrae and the skin becomes closed off from the rest of the canal and remains a cavity, which is lined with that part of the epidermis which has been segregated to form the central

14. Rienhoff, W. F.: Congenital Arteriovenous Fistula. Bull. Johns Hopkins Hosp. 25:271, 1924.

nervous system. This cavity or cystic space may be situated near the skin with an opening or openings onto the surface of the skin, or may be near the periosteum of the sacrococcygeal union without any connection with or opening onto the skin. This blind pouch of the neural canal will, by cohesion of its walls and subsequent obliteration, disappear about the sixth month. However, this structure may persist into post-natal life, as has been demonstrated by Mallory,<sup>2</sup> Tourneaux, Keibel and Mall<sup>10</sup> and Oehlecker.<sup>4</sup> That part of the neural canal proximal to this closed-off end becomes obliterated and forms a solid cord which is known as the filum terminale.

This canal, which is lined by epidermal tissue, has no function as regards the development of nervous tissue; therefore, it may fail to obliterate and remain patent in part or in whole. If this condition should exist, a connection of this canal with the cystic cavity mentioned in the foregoing paragraph would be present which would consist of an epithelial-lined canal extending for various depths toward the conus of the spinal cord from an opening on the cutaneous surface in the sacrococcygeal region. The depth to which this patent canal may extend varies. It may extend to the hiatus of the sacral canal, may penetrate this covering of the hiatus and extend into the sacral canal from just beneath the sacral hiatus up to the dura, or it may be continuous with the spinal cord. That such an anomaly does exist has been demonstrated in cases reported in the literature and also in one of the cases reported in this paper.

That similar conditions exist in the embryo and persist into postnatal life is well known. Analogous changes occur in the formation, development and descent of the testicle with its tunica vaginalis. If that part of the peritoneum forming the tunica vaginalis fails to obliterate, there remains a patent canal extending from the peritoneal cavity to the base of the testicle. This formation explains the preformed sac in congenital indirect inguinal hernia. If the canal is closed only at the internal ring, a large hydrocele develops, because the cells lining the unobliterated tunica are secretory. When the tunica is obliterated partially, from the testicle toward the internal ring, or if it is patent for a short distance along the cord, various types of hydrocele of the cord occur. Where similar epithelial-lined canals fail to obliterate normally they may remain patent in part or in whole. This has been demonstrated embryologically and clinically in various organs and tissues of the body.

(b) A complete understanding of the epidermis, its formations and developmental peculiarities in the formation of the nervous system and the skin appendages is important: The epidermis by a process of infolding forms the neural canal; the individual characteristics of the epidermal cell are then lost by a process of cellular division and differentiation, resulting in the formation of the nerve tissue that will form the

future brain and cord. In the caudal end of the neural canal a different process takes place. As the caudal end of the canal obliterates and forms a cord of tissue recognized postnatally as the *filum terminale*, the epidermis that forms this canal takes no part in the formation of the true spinal cord. Therefore, if nerve tissue should develop from this part of the canal it would be rudimentary and more or less embryonic, and no definite nervous structure would be formed.

The neural canal is completely formed before the appearance of the most primitive of the appendages of the epidermis, i. e., hair shafts. The sebaceous glands appear next at a time which corresponds to the second or third month of embryonic life, after the fetus is fully formed. The sweat glands do not appear until the fifth month and are completely formed about the seventh. Therefore, the entire nervous system has differentiated into its component parts and is completely formed, the neural canal is obliterated and the *filum terminale* has anchored the spinal cord to the first segment of the coccyx or to the dorsal surface of the coccygeal vertebrae before all of the appendages of the skin occur.

If there has been a failure of the blind pouch or cystic cavity to obliterate in its entirety there remains a cavity lined by epidermis that was intended to form the caudal part of the neural canal. Therefore, it has lost its totipotentiality of the true epidermis, and if appendages develop at all they will be most rudimentary. As no appendage makes its appearance before the second month, and as the neural canal has been closed off before this time, the epidermal lining of this cystic cavity in all probability retains the power to form the most primitive appendage, the hair follicle and hair shaft. This same condition would exist if the neural canal failed to obliterate distal to the sacrococcygeal union. One would expect to find a canal lined with epidermis containing no appendages with the exception of hair and hair follicles (fig. 1). If, however, the neural canal failed to obliterate and extended into the sacral canal, was attached to the dura or was continuous with the spinal cord, the power to form appendages would in all probability be completely lost, and there would be only an undeveloped epidermis.

Therefore, the nearer to the spinal cord this part of the caudal canal remains unobliterated, the more closely will it be associated with the formation of nerve tissue, and in some instances it should be possible to find rudimentary or embryonic nerve tissue along the patent canal.

All of these findings I have been able to demonstrate microscopically in a large number of sections of surgically removed pilonidal sinuses. By differential staining in one instance in which the neural canal was patent up to the dura, I have demonstrated embryonic nerve tissue just beneath the epithelial lining of the canal (figs. 2 and 3). The epidermis

lining the canal did not reveal a single appendage of the true skin, which was anticipated. The finding of this nerve tissue was confirmed by staining the section with Masson's stain. The character of this tissue was determined by staining the tissue section with phosphotungstic acid hematoxylin. The latter stain demonstrated the fine fibrils running in the mass of young nerve cells to be neuroglia fibrils. The demonstration of the presence of embryonic nerve tissue along that part of the unobliterated neural tube located in the sacral canal has a



Fig. 1.—Photomicrograph through the center of the sinus showing the sinus tract lined by squamous epithelium. The epithelium has been desquamated and eroded as shown in the lower left corner. There are no sebaceous or sweat glands in this section. Hair shafts can be seen in the lumen of the sinus.

most important bearing on the origin of the pilonidal sinus from the neural canal as well as the development of gliomas in the sacrococcygeal region.

(c) The last caudal vertebra is attached to the skin by a prolongation of the mesoderm from the tip of the last coccygeal vertebra to the epidermis. Because the vertebrae grow more rapidly than the overlying

skin the caudal ligament becomes reflected dorsalward, and at the third or fourth month the skin which is attached to the caudal ligament lies over the third or fourth caudal vertebra. According to Oehlecker, the site of attachment of the caudal ligament to the skin marks an area in the skin ("sacral bald spot") that is devoid of hair and is vascular. If the development of the caudal ligament does not proceed normally with the upward progress of the skin, owing to the rapid downward development of the caudal vertebrae, the ligament remains short and the

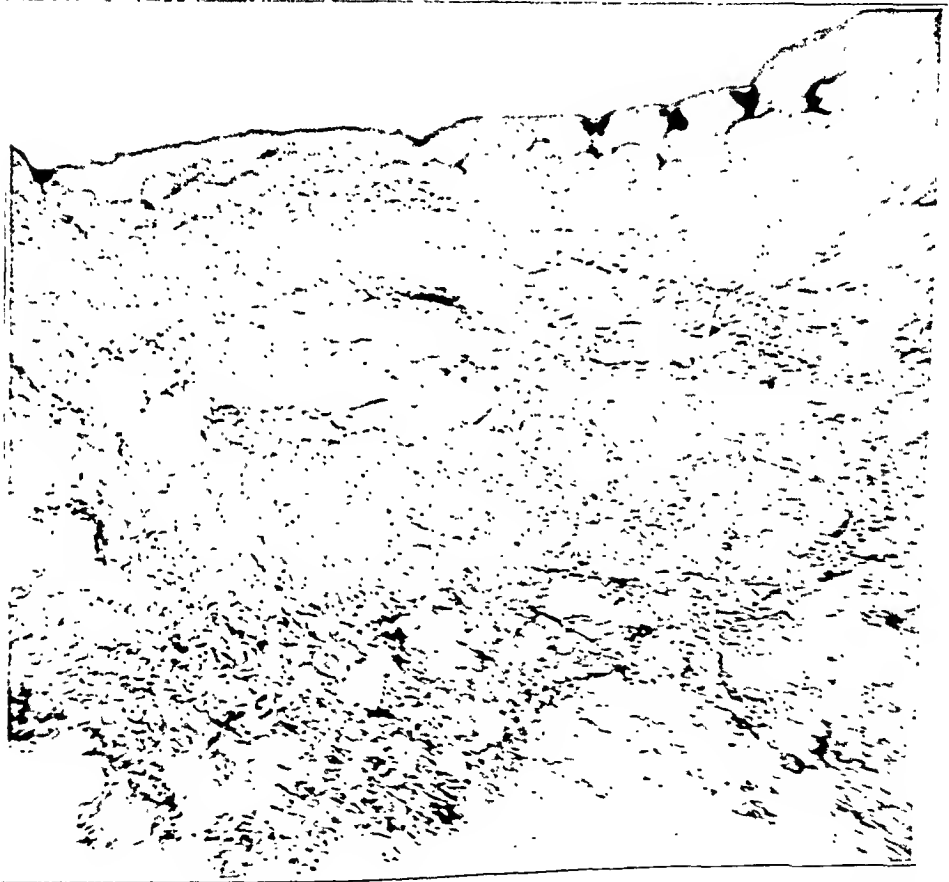


Fig. 2.—Photomicrograph of section taken from the sinus tract within the sacral canal. This shows the edge of the sinus tract lined by squamous epithelium. There are no hair shafts, hair follicles, sebaceous or sweat glands. The arrows point to an area of embryonic gelatinous tissue, which is just beneath the epithelial lining of the tract.

overlying skin is retracted toward the coccyx by the pull of this ligament, which produces a depression or dimple. The ligament finally becomes a part of the periosteum over the coccygeal vertebrae, and the skin becomes fixed to the deep connective tissue by this attachment. As the buttocks grow outward in their normal process of development there remains a depression in the overlying skin, this depression being known

as the sacrococcygeal dimple. If this dimple persists into adult life, the lower end of the dimple will be pulled in deeper than the more cephalic part. This increasing pull produced mainly by the skin fixation and increasing bulk of the nates, will change the dimple into a funnel-shape sinus with the lowermost part pointing toward the anus. There may develop an overlying bridge of skin which can produce a condition similar to the true type of patent neural canal.



Fig. 3.—Photomicrograph, low power, showing area of embryonic nerve tissue depicted in figure 2, stained by Masson's differential stain.

That this developmental defect occurs as described in the foregoing paragraph has been demonstrated both embryologically and postnatally. The sacrococcygeal dimple has been demonstrated in both children and adults by many investigators as well as in two cases which are now reported:

In case 1, that of a child, this developmental defect was represented by a coccygeal dimple about 0.5 cm. deep. That it was due to the pull of the coccygeal ligament was demonstrated at operation, because section of the connective tissue fibers beneath the dimple allowed the dimple immediately to lose its depression and smooth out level with the normal contour of the surrounding skin.

In case 2, that of an adult, there was a sinus at the lower end of the dimple. Surgical removal revealed in the gross specimen a band of connective tissue fibers that were attached to the under surface of the epidermis, exerting a downward pull on the skin, which was responsible for the dimple and for the sinus formation. Study of sections from both failed to reveal hair shafts or follicles.

These two observations corroborate the findings of Oehlecker, who demonstrated the sacrococcygeal dimple in the embryo, and termed it the "sacral bald spot."

I believe that conclusive evidence has been presented to show that the sacrococcygeal dimple and the pilonidal cyst develop from two separate and distinct embryologic developmental defects. The sacrococcygeal dimple results from anomalous development of the caudal ligament and its attachment to the skin. This developmental anomaly can be traced from the embryo to the postnatal adult stage, and histologic examination of tissue removed from this defect found clinically in the adult corresponds exactly to the histology of the sacral dimple found in the embryo. That the various types of pilonidal cysts are results of embryologic developmental defects occurring in the caudal end of the neural canal I believe to be an established fact.

The clinical types described in the literature could hardly occur if there were not a preexisting sinus or canal from which the postnatal sinuses could develop, and this preexisting sinus or canal is represented in the embryo by the neural canal. Conclusive evidence has been found in the cases of pilonidal cyst occurring in adults, in which the tract of the sinus may extend from an opening in the skin of the sacral area to the sacrococcygeal membrane or into the sacral canal for varying distances. It may extend to the dura or may even be continuous with the spinal cord. Normal epidermal appendages, except hair follicles, could hardly develop from cells that have been differentiated to form another organ before the embryologic development of these appendages begins. This has been substantiated by a study of the specimens removed at operation. There are no appendages except hair shafts developing from the epithelial lining of the sinus tract. The epithelial lining of the sinus that approaches the spinal cord produces no appendages. The finding of embryonic neuroglia cells and fibrils associated with the sinus tract in the sacral canal could not be explained unless they had developed from the embryonic neural canal. Therefore, I believe that the various clinical types of pilonidal sinus have their origin from the caudal end of the neural canal.

I have divided the clinical cases of pilonidal cysts and sinuses into four groups, in order to facilitate the diagnosis of such conditions and as an aid in their treatment. I believe that this grouping as regards treatment will have a great tendency to prevent recurrences, which ordinarily vary between 30 and 50 per cent.

Group 1. In this group are included all the cases of sacrococcygeal dimple. This anomaly is the simplest both embryologically and clinically. The cyst or sinus is superficial, and the tract does not penetrate to the periosteum of the sacrum or coccyx.

Group 2. In this group are included the cases of true pilonidal sinus. The sinus usually extends for varying depths from the skin; it may be situated just beneath the skin, or it may extend down to the periosteum of the sacrum or coccyx. It may have a bulbous dilatation at either end, just beneath the skin or near the periosteum of the sacrum.

Group 3. In this group are included the cases in which the sinus extends down between the sacrum and coccyx or enters the sacral canal for varying distances, even extending to the dura at the level of the second sacral vertebra. The site of the cutaneous opening of the sinus varies in position but corresponds to the closure defects of the bony covering of the sacral vertebrae.

Group 4. In this group, the rarest of all, are the cases in which the sinus is complete and communicates with the spinal cord. Cerebrospinal fluid is discharged from the sinus in varying amounts. The amount, however, is usually very small.

#### ILLUSTRATIVE CASES

A few selected cases will now be presented, corresponding with the foregoing classification.

*Type 1.*—CASE 1.—J. L., a girl, white, aged 8 years, was admitted to the hospital on June 20 and was discharged on Aug. 12, 1933. The chief complaint was of a dimple of the coccygeal region. Examination revealed a small dimple situated above the dorsal aspect of the coccyx near its junction with the sacrum. The dimple was about 0.5 cm. in diameter and extended below the surface of the skin for about 0.5 cm. No sinus was present.

Under local anesthesia, an elliptic incision revealed fibrous connective tissue bands extending from the under surface of the dimple to the coccyx. Following division of these fibers the dimple immediately disappeared and flattened out level with the surrounding skin. This observation confirms that of Oehlecker, and is definite proof that the dimple was caused by a pull of the coccygeal ligament on the skin.

The histologic examination revealed no hair follicles in the skin removed.

CASE 2.—E. T., a white man aged 31 years, was admitted to the hospital on October 16 and was discharged on Nov. 3, 1933. He complained of pain over the coccyx which had been present for three months. About three weeks after the onset of pain, the patient noticed a yellowish discharge from the coccygeal area.

Examination showed a shallow sinus over the coccyx, extending toward the anus. There were two sinuses discharging pus on the right side of this dimple. The lower sinus had a small papilloma at its exit on the skin. Both sinuses communicated with the coccygeal sinus.

At operation, under gas anesthesia, the dimple with its accompanying sinuses was removed by an elliptic incision which extended down to the coccyx. The wound was closed, with drainage.



Gross examination of the specimen revealed a typical coccygeal dimple with radiating strands of connective tissue attached to the skin and extending downward to the coccyx. There was a small sinus at the inferior part of the dimple, due to the pull of these connective tissue strands.

On histologic examination, the sinus was found to be lined by epithelium without the presence of hair or hair follicles. A chronic inflammatory reaction was present.

In these cases the lesion was a coccygeal dimple produced by the pull of the coccygeal ligament on the skin.

*Type 2.*—CASE 3.—E. V., a white man, aged 24 years, was admitted to the hospital on October 4 and discharged on Oct. 16, 1933. His chief complaint was of a discharging sinus between the buttocks. Examination revealed a discharging sinus in the area of the sacrococcygeal region. There were five sinuses in a straight line in the midline over a distance of about 3 cm. A diagnosis of pilonidal cyst was made.

At operation, the entire area containing the sinuses was removed by an elliptic incision which extended down to the periosteum of the sacrococcygeal region. The wound was closed with interrupted silkworm gut sutures, with a rubber drain at the lower angle. Except for a small area of skin, the wound healed by primary intention.

Examination of the gross specimen showed two cystic cavities about 1 cm. in diameter, connected with each other by a sinus about 0.25 cm. in diameter and about 1 cm. long. These two cysts and the connecting sinus were situated just beneath the skin and connected with it by five openings, two openings leading into the upper cyst and three into the lower cyst. These cystic cavities and the sinus did not extend more than 1 cm. below the skin surface.

Histologic examination revealed that both cystic cavities were lined by stratified squamous epithelium. Numerous hair follicles but no sebaceous or sweat glands were present. This condition corroborates the description of pilonidal cysts by Tourneaux as "*vestiges coccygiens reflecti*." This cyst presented both clinical and histologic evidence of having had its origin from the terminal portion of the medullary canal.

CASE 4.—B. A., a white youth aged 17 years, was admitted to the hospital on April 5, was operated on April 6 and discharged on April 17, 1933. He complained of pain in the sacral region. Six months previously, he injured his back in the region of the sacrum. An abscess developed after the injury which soon ruptured and drained. After that he had intermittent pain in the sacral region. Examination showed two small sinuses near the sacrococcygeal joint. A probe inserted into each extended for about 2 cm. toward the sacrococcygeal hiatus. The diagnosis was pilonidal sinus.

At operation, under ether anesthesia, an elliptic incision, 10 cm. long, circumscribing the sinus area, was made. The entire mass was excised, and the sinus tract was found to extend to the periosteum, but did not involve it. The wound was closed, with drainage. The patient made an uneventful recovery.

Microscopic examination showed a chronic inflammatory reaction around the sinus tract. Hairs and hair follicles were present, but no sebaceous or sweat glands.

This case is one in which the medullary canal failed to close, resulting in the formation of a sinus that extended from an opening on the skin down to the periosteum of the sacrum.

*Type 3.*—CASE 5.—Z. F., a woman aged 30 years, was hospitalized on April 8 and discharged on June 6, 1933. This patient was operated on two years pre-

viously for a pilonidal sinus, at which time the sinus was dissected down to the sacrococcygeal region and the coccyx removed. The wound took several weeks to heal.

On readmission to the hospital she complained of a discharging sinus in the region of the old operation. Examination revealed a scar in the sacrococcygeal region with a sinus in the scar. The patient was operated on, on June 15. The sinus was dissected with the scar tissue extending down into the sacral region. The sinus and the surrounding tissue were represented by a cordlike structure about 0.5 cm. in diameter. After careful dissection into the sacral canal, the tissue was pulled on and severed with scissors; there was an immediate gush of cerebrospinal fluid into the wound. The entire wound was packed with iodoform gauze and loosely closed with sutures.

Histologic examination of this tissue revealed a sinus tract, lined by stratified squamous epithelium, incompletely developed. There were no skin appendages, hair, sebaceous glands or sweat glands present. An important finding in the sinus tract was that of embryonic nerve tissue, which by differential staining proved to be neuroglia.

The patient recovered and the wound was completely healed at the time of her discharge from the hospital.

*Type 4.*—CASE 6.—Moise<sup>15</sup> reported a case of staphylococcic meningitis secondary to a congenital sinus. The patient, a white youth aged 18 years, since birth had had a persistent sinus situated over the upper part of the sacrum. It communicated with the spinal cord, and discharged a watery fluid intermittently. At operation, by injecting methylene blue into the sinus, it was found to communicate with the spinal canal. Continuous drainage was established by resecting the sinus and performing a laminectomy. The patient recovered.

There was associated with this sinus a congenital malformation of the sacrum which Moise interpreted as spina bifida occulta.

This case represents one of the rarest types of pilonidal cysts, one in which there was complete failure of obliteration of the caudal end of the medullary canal. The sinus tract was lined by stratified squamous epithelium, but no mention was made of the presence of skin appendages.

CASE 7.—Ripley and Thompson<sup>16</sup> reported a case of staphylococcic meningitis occurring in a child, 3½ months old, secondary to a pilonidal cyst located over the second sacral vertebra. In this case the sacral arch was deficient. The sinus led from the skin to a sac over the second sacral vertebra. The sac contained hair and sebaceous material. The base of the sac communicated with the spinal cord, an observation which was verified at autopsy. The child had a defect in the arches of the sacrum as well as a pilonidal sinus in the region of the second sacral vertebra. The sinus communicated with the spinal canal and was the portal of entry in the development of meningitis of the staphylococcic type.

The cases cited by Moise and Ripley and Thompson represent cases in group 4, in which the embryologic defect consists of failure of obliteration of the caudal end of the medullary canal.

15. Moise, T. S.: Staphylococcus Meningitis Secondary to Congenital Sacral Sinus, *Surg. Gynec. & Obst.* 42:394, 1926.

16. Ripley, W., and Thompson, D. C.: Pilonidal Sinus as Route of Infection in Case of Staphylococcus Meningitis, *Am. J. Dis. Child.* 36:785 (Oct.) 1928.

# INTRADIPLOIC EPIDERMOID (CHOLESTEATOMA) OF THE SKULL

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Epidermoids are relatively rare neoplasms which occur most frequently in and about the nervous system, particularly in its cranial portion. They have been called cholesteatomas, *tumeurs perlées*, *Perlgeschwulst* and atheroma. They may arise beneath the scalp, within the diploe, between the bone and the dura mater, beneath the arachnoid membrane, particularly about the base of the brain, or within the ventricles. It is now commonly accepted that these tumors arise from ectodermal rests—a hypothesis originally advanced by Remak<sup>1</sup> in 1854, although it was not universally accepted until many years later. Such embryonic rests are probably remnants of an incomplete separation of the neural from the surface ectoderm. Such epithelial anlagen when located within or near the nervous structures form the intraventricular and subarachnoid epidermoids. At other times they have been deposited between the two ectodermal structures, skin and brain, and surrounded by mesodermal tissues, thus forming the epidural, intradiploic and epicranial tumors. It is of interest to note that when such embryonal rests maintain their connection with the surface epithelium, which they seem to do most frequently in the spinal region, they form congenital dermal sinuses which may be the pathway for the entrance of infection into the meninges, producing subdural abscesses and meningitis.<sup>2</sup>

In this report I am primarily concerned with those epidermoids which arise within the diploe of the skull. These are rare, only thirteen having been reported in the literature, with the three reported here making a total of sixteen. In this connection it should be noted that similar tumors may arise in connection with the middle ear and the frontal sinuses which are undoubtedly closely related to the condition in the cases reported here. However, as the extensive literature dealing with them is greatly confused by the problem of the masses of infectious débris known as pseudocholesteatomas which arise in these regions,

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1. Remak, R.: Ein Beitrag zur Entwicklungsgeschichte der krebshaften Geschwülste, *Deutsche Klin.* 6:170, 1854.

2. Walker, A. E., and Bucy, P. C.: Congenital Dermal Sinuses, *Brain* 57: 401, 1934.

particularly in and about the ear, these tumors will be omitted from the discussion and left in the province of the otologist and rhinologist.

Intradiploic epidermoids, though frequently large and commonly compressing the brain, are rarely productive of neurologic symptoms. The clinical and roentgenologic picture which they cause is, however, typical and hardly to be confused with any other condition. On examination one usually finds a swelling on the surface of the skull which has, in the majority of cases, been observed in some degree for many years, commonly from childhood. It is associated with a palpable defect in the skull, the edges of which are often raised, forming a bony ridge about all or part of the tumor. The mass is soft, may be fluctuant and may pulsate, depending on the intactness of the internal table of the skull. Roentgen examination reveals a defect in the bones of the skull which may or may not be regular. The margins of the defect may have a scalloped appearance, particularly well shown in King's first case.<sup>3</sup> The defect is caused by the tumor which arises within the diploe spreading and eroding the inner and outer tables of the skull. At operation an encapsulated cyst is found, the contents of which consist of white lamellae presenting the appearance of mother-of-pearl and a more or less extensive whitish-yellow caseous mass. The capsule is invariably thin and friable and is often separated from its bony crater and the dura mater with difficulty. For this reason Cushing<sup>4</sup> advised the reflection of an osteoplastic flap which completely included the bony defect in order that the tumor might first be separated from the dura mater and then removed from its bony crater intact. This is undoubtedly the procedure of choice when the outer table is only elevated and but slightly eroded whereas the inner table has been destroyed, but in cases in which the reverse is true, as in the cases reported here, it is hardly necessary. It is important, however, that the wall of the cyst, composed of a stratified squamous epithelium which is the only living, growing part of the neoplasm, be removed completely in order to prevent recurrence. Simple evacuation of the cyst will not suffice.

In addition, Sir Percy Sargent was wont to point out that even though the inner table of the skull seems intact it is almost invariably fractured or eroded over a small area. Through this defect the tumor

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3. King, J. E. J., cited by Horrax, G.; Yorshis, M., and Lavine, G. A.: Calcified Intradural Cholesteatoma of Unusual Size in a Patient Showing Manic-Depressive Symptoms, *Arch. Neurol. & Psychiat.* **33**:1058 (May) 1935; personal communication to the author.

4. Cushing, H.: A Large Epidermal Cholesteatoma of the Parieto-Temporal Region Deforming the Left Hemisphere Without Cerebral Symptoms, *Surg., Gynec. & Obst.* **34**:557, 1922.

tends to extend beneath the bone, between it and the dura mater. At operation one should, therefore, always explore the epidural space beneath the bone in order to be certain that all the tumor has been removed.

Through the kindness of the late Sir Percy Sargent, who supplied the notes concerning cases 2 and 3 from his personal records, and of Dr. Gordon Holmes I have been permitted to report the following three cases of intradiploic cholesteatoma which clearly illustrate the symptomatology, course, observations and proper treatment in cases of this rare tumor.

#### REPORT OF CASES

*CASE 1.—Swelling in right parietal region from before the age of 5 years. Slow increase in size. Asymptomatic until the age of 28, when convulsions appeared on the left side. Rachitic dwarf with defect in right parietal bone occupied by soft tumor and surrounded by bony ridge. Operation: removal of epidermoid of skull. Recovery.*

*History.*—R. W., a waiter, aged 28, was admitted to the service of Dr. Gordon Holmes at the National Hospital for Nervous Diseases on Feb. 10, 1931. He complained of a swelling on the right side of the head and of a convulsive seizure which had occurred on January 17. The patient stated that the swelling on the right side of the head was present prior to the age of 5 years, and his mother insisted that it was not present at birth. During the succeeding years it had grown slowly, but in no other way had its presence been manifested. It had often been struck while the patient was in school, in the boxing ring and elsewhere, but this had never been associated with any symptoms either local or general.

The family history was irrelevant. The patient had suffered from severe rickets in childhood, but otherwise his past history, except as noted, was unimportant.

*Jacksonian Convulsion.*—On January 17, while working at his trade as a waiter, the patient suffered from his first, and only, "fit." Warning of the approach of this attack was given by a sensation of "pins and needles" in the finger-tips of the left hand. This paresthesia then spread up the arm to the shoulder, into the left side of the neck and jaw. The left hand then contracted, the wrist and arm flexed, and the entire extremity was raised at the shoulder. At no time was there any tremor or clonic movement. The patient found himself unable to extend the arm, and the sensation of pins and needles continued. He then asked a fellow waiter to straighten his arm, and this endeavor caused pain in his neck and jaw. At this point in the attack the patient lost consciousness. This lasted a few seconds, and on recovery the arm was relaxed and the paresthesia was gone. There was, however, a feeling of stiffness in the left side of the neck and jaw, and they seemed drawn to the left. The patient also noted a dull ache in the swelling on the right side of the head. Observers stated that during the period of unconsciousness there was no convulsion but the patient became very dark. He soon recovered completely and consulted his physician who referred him to the National Hospital.

*Examination.*—The patient was a rachitic dwarf. The lower extremities were short and both, especially the right, were markedly bowed. When he was standing the finger-tips reached to the knees. Palpation of the skull revealed a soft fluctuant swelling in the center of the right parietal bone measuring  $1\frac{1}{2}$  by  $1\frac{1}{4}$  inches

(3.7 by 3.1 cm.) and elevated about  $\frac{3}{4}$  inch (1.9 cm.) above the plane of the surrounding tissues. The margins of the swelling were irregular and bony hard, and in the antero-inferior portion they projected above the level of the skull. There was very slight pulsation, and deep palpation elicited a cracking sound. Except for these findings the remainder of the physical examination gave negative results, and no evidence of involvement of the nervous system could be detected.

Lumbar puncture showed the cerebrospinal fluid pressure to be 195 mm. of fluid, and there were two cells per cubic millimeter and a total protein content of 50 mg. per hundred cubic centimeters of fluid.

The right lateral roentgenogram of the skull (fig. 1) disclosed a large ovoid defect in the upper half of the parietal bone. The margins were quite regular and slightly increased in density. The anteroposterior view (fig. 2) demonstrated the same defect. The separation of the inner and outer tables of the skull by the



Fig. 1 (case 1).—Right lateral roentgenogram of the skull. There is a large oval defect in the right parietal bone, the margins of which show a slight increase in density.

tumor was particularly well demonstrated. The inner table which formed the floor of the bony crater was depressed into the cranial cavity. The outer table had been completely eroded over a large area, but along the lower margin of the defect it formed an elevated overhanging ledge of bone. This was palpable clinically.

The patient was seen by Sir Percy Sargent, who immediately on examination and study of the roentgenograms made a diagnosis of cholesteatoma of the skull. The basis for his diagnosis was the recollection of two cases of intradiploic epidermoid in which he had performed an operation. In his cases there was a defect in the skull occupied by a soft tumor which arose within the diploe, separated the inner and the outer table of the skull and partially eroded the latter, thus producing a bony ridge about the opening.

*Operation and Course.*—On March 20, Sir Percy Sargent operated on the patient, making a semicircular flap of the scalp with the tumor at the center. This

was reflected, and beneath it was found a firm white cyst containing caseous white material. The cyst had excavated a circular crater about 2 inches (5 cm.) in diameter in the parietal bone. The cyst was readily enucleated. Beneath it was a very thin plate of bone, the inner table, which was greatly depressed and was broken by a stellate fracture. This inner table was removed, and lying between it and an irregularly thickened dura was more caseous material which was readily removed.

The patient made a complete recovery from the operation and was discharged on April 17.

*Microscopic Examination.*—A single section of the rolled-up wall of the cyst fixed in solution of formaldehyde and stained with hematoxylin and eosin (fig. 3) is available. The wall was composed of three distinct layers. The outermost was relatively acellular connective tissue which acted as the supporting



Fig. 2 (case 1).—Anteroposterior roentgenogram of skull. The defect is seen in about the middle of the right parietal bone. The neoplasm has separated the two tables of the skull. The outer table, which has been elevated above the surrounding bone, is partially eroded, the remaining antero-inferior portion forming an overhanging ledge. The inner table is intact and has been depressed into the intracranial cavity.

framework for the epithelial layer. Within this connective tissue were scattered fusiform and stellate fibroblasts, between which was a mass of intercellular fibers, reticulin and collagen. Throughout this layer were a few small blood vessels. Immediately internal to this lay the second layer, which was composed of a relatively thin stratified squamous epithelium. This layer was for the most part about six cells thick, though in places it increased to as much as fifteen or twenty cells. The deepest layer of this epithelium was composed of polyhedral or cuboidal cells arranged perpendicular to the plane of the epithelial layer. These cells corresponded to the malpighian cells in the basal layer of normal epidermis. Superficial to this layer the cells were much more flattened than those of normal epidermis and lay

parallel to the surface. The third layer consisted of cornified epithelium. It was composed of yellowish fibers arranged parallel to the surface and devoid of nuclei. The epithelial tissue was devoid of papillae and there were no dermal structures such as hair and glands. Microscopically this was a typical epidermoid.

In this case there was the typical history of long duration of a swelling of the scalp associated with a defect in the skull which was

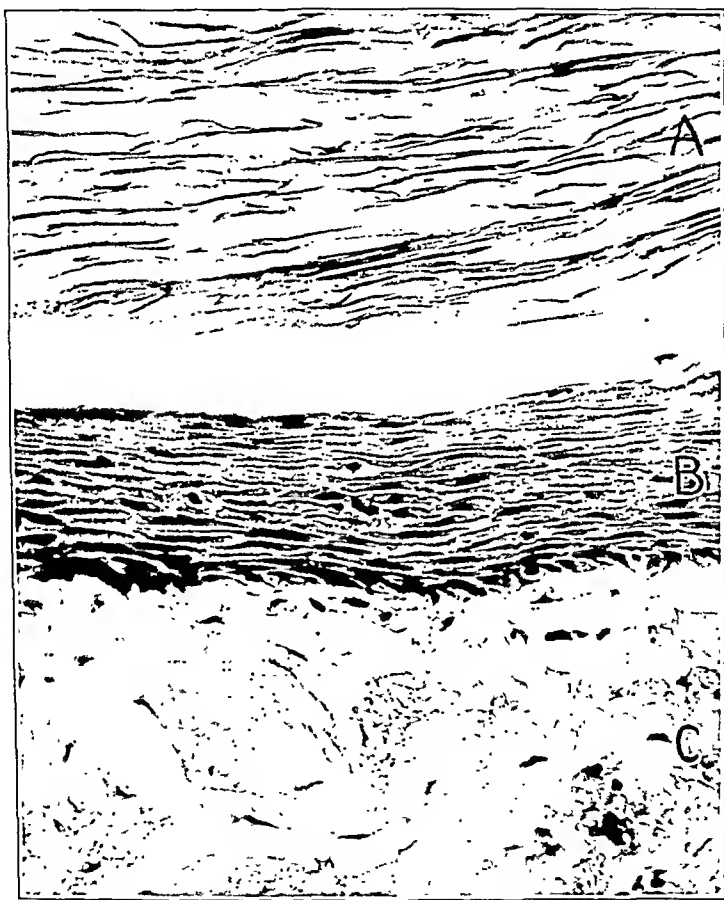


Fig. 3 (case 1).—Photomicrograph of the lining of the epidermoid cyst. Three layers are seen: *A* is composed of cornified epithelial cells which fill the interior of the cyst; *B* is a layer of stratified squamous epithelium, and *C* consists of relatively acellular connective tissue. Hematoxylin and eosin stain;  $\times 380$ .

clearly demonstrable in the roentgenogram. It was unusual only in its association with a localized convulsive seizure which must be attributed to the effect of the tumor on the underlying central area of the right cerebral hemisphere. The microscopic picture was typical of these tumors.



CASE 2.—*Swelling in left frontal region of eighteen months' duration. Bony defect with raised bony margins. Operation: partial extirpation of cholesteatomatous epidermoid. Apparent recurrence three years later.*

C. G., a woman aged 26, first noted a swelling just to the left of the midline in the forehead eighteen months before consulting Sir Percy Sargent. This slowly increased in size until at the time of surgical intervention it measured  $1\frac{1}{2}$  inches in diameter. It had caused no other symptoms. Examination revealed a fluctuant swelling which did not pulsate and was not translucent. It was definitely surrounded by a ridge of bone. Roentgenograms revealed a rounded bony defect in the left frontal region.

*Operation.*—On Oct. 9, 1929, Sir Percy Sargent operated on the patient at St. Thomas's Hospital. The tumor lay in a bony crater with elevated margins in the frontal bone. The floor was depressed and very thin and was defective in the center. Through the opening the tumor was continuous with an endocranial portion which lay between the dura mater and the bone. Most of the caseous material was removed as well as the elevated bony margins of the crater and part of the inner table. The patient made an uneventful recovery and was discharged, returning to her work as a secretary.

*Recurrence.*—I was fortunate enough to see this patient in May 1931. She had remained in excellent health following the operation and continued satisfactorily with her work. She stated that following the operation the site of the tumor was depressed but subsequently this depression gradually filled in. Examination revealed a soft swelling in this region which was elevated slightly above the surrounding skin. The swelling presumably is a recurrence due to failure to extirpate the wall of the cyst completely.

Unfortunately no microscopic preparations are now available.

This case in all probability is indicative of the necessity of removing the entire cyst, contents and wall, at operation. If small portions of viable epithelium are left there must always be a danger that the tumor will recur.

CASE 3.—*Swelling in frontal region of many years' duration. Tumor resting in bony defect with raised bony margin. Operation: removal of intradiploic epidermoid. Recovery.*

E. S., a man aged 39, had long noted a swelling in the midline of the frontal region just above the bregma. This had apparently increased in size following a blow some time prior to his admission to St. Thomas's Hospital. There were no other symptoms.

Examination revealed a swelling in the middle of the forehead measuring  $2\frac{1}{2}$  inches (6.2 cm.) vertically and  $1\frac{1}{2}$  inches across which was elevated about 1 inch (2.5 cm.) above the surrounding tissue. A ridge of bone was palpable at the margins. This swelling was nonfluctuant and did not pulsate or transmit light. Apparently a roentgenogram was not made.

*Operation.*—On Jan. 29, 1930, Sir Percy Sargent operated on this patient and found a cyst lying in a bony crater. The cyst was readily shelled out and was found connected by a pedicle which passed through the thin, defective inner table to another collection of cholesteatomatous material within the skull. The cyst contained typical caseous material. The patient made an uneventful recovery and was soon discharged. Nothing is known of the subsequent course.

Unfortunately no microscopic preparations are available.

There can be little question of the nature of the neoplasm in cases 2 and 3 in spite of the absence of microscopic preparations. The clinical picture presented was typical of this condition, and the diagnosis was made by Sargent, who was thoroughly familiar with the appearance of such tumors.

In case 1, although the tumor had been subjected to repeated traumatic injury, the patient attached little significance to this fact. And there was no apparent relationship between injury and the growth of the neoplasm or the development of symptoms. In case 2 there was no mention of any injury. In the third case the patient, while not attributing the tumor to trauma, felt that an injury precipitated an increase in its size. It seems entirely unlikely that the growth of a neoplasm arising deep within the bone and explicable purely on the basis of an embryologic malformation should be precipitated by injury.

#### REVIEW OF THE LITERATURE

The first accurate description of a cranial epidermoid must be attributed to Cruveilhier,<sup>5</sup> in 1829, although it appears that Leprestre and Dupuytren had previously described such neoplasms. Nine years later, in 1838, Johannes Müller<sup>6</sup> in his excellent monograph described additional cases, among which was the first example of an intradiploic epidermoid to find its way into the literature. It is interesting to note that Müller observed the striking similarity between the contents of these cystic tumors and the cornified layer of the skin. He failed, however, to attribute these tumors to the epidermis correctly because of an incomplete examination of the walls of the cysts, which he thought consisted of acellular connective tissue. Remak<sup>1</sup> in 1854 was the first to correlate these neoplasms definitely with the epidermis, although his views regarding this association were not universally accepted until many years later.

Sixteen cases of epidermoid arising within the diploe have been described. These have been briefly summarized in the accompanying table. It will be noted that certain cases referred to by other writers as being instances of this type of growth have been omitted from the table. The case reported by Pfannmüller<sup>7</sup> was one of a subarachnoid epidermoid of the temporal lobe which did not involve the skull. In the

5. Cruveilhier, J.: *Anatomie pathologique du corps humain*, Paris, J. B. Baillière, 1829, vol. 2, pt. 1, plate 6.

6. Muller, Johannes: *Ueber den feinen Bau und die Formen der krankhaften Geschwulste*, Berlin, G. Reimer, 1838.

7. Pfannmüller, W.: *Ueber das meningeale Cholesteatom*, Inaug. Dissert., Giessen, C. von Munchow, 1896.

*Cases of Intradiptloic Epidermoid Tumor (Cholesteatoma) of the Skull Reported in the Literature*

Author	Sex	Age When Diagnosed	Age at Onset	Region	Size	Symptoms	Erosion			Pulsation
							Outer Table	Inner Table	Bony Ridge	
1. Müller <sup>6</sup> (1838) .....	..	..	..	Occipital	.....	.....	Partial	+	..	..
2. Esmarch, Virchow's Arch f. path. Anat. 10 : 307, 1856	M	24	10	Left frontal	2.5 cm. high, 5.5 cm. in diameter	None	+	Broken	+	..
3. Weinlechner: Wien. klin. Wehnschr. 2 : 136, 1889	M	45	12	Left frontal	.....	Convulsions; headache	Small	+	..	+
4. Wotruba: Wien. klin. Wehnschr. 2 : 899, 1899	M	22	15	Right frontal	Goose egg	Headache; impaired vision by direct pressure on eye	+	+	..	..
5. Blecher: Deutsche Ztschr. f. Chir. 70 : 353, 1903	M	23	Since childhood	Left parietal	Hen's egg; 1.5 by 4 cm.	Headache	+	Small defect	+	0
6. Unterberger: Deutsche Ztschr. f. Chir. 81 : 50, 1906	F	16	2	Left sphenoidal and frontal	.....	Headache	+	+	+	0
7. Cushing <sup>4</sup> (1922) .....	M	40	24	Left temporo-parietal	3½ in. in diameter	? none	Small	+	+	+
8. Orlandi: Virchow's Arch. f. path. Anat. 237 : 169, 1922	M	71	?	Right parietal	5 by 3 cm.	?	+	Small	+	?
9. Kempmann: Beitr. z. klin. Chir. 139 : 343, 1927	F	40	49	Left parietal	Palm of hand	0	+	+	+	?
10. Wertheimer: Fortschr. a. d. Geh. d. Röntgenstrahlen 38 : 656, 1928	M	38	Accidental finding	Right frontal and sphenoid	?	0	+	+	?	?
11. Alpers and Harrow: Am. J. Surg. 18 : 51, 1932	F	52	40	Right occipital	Large	Impaired vision, headache, nausea, vomiting	+	+	?	?
12. King <sup>3</sup> .....	M	28	23	Right temporo-parietofrontal	7 by 5 by 4 cm.	Weakness left leg, blurred vision, diplopia, left hypesthesia	Partial	+	+	0
13. King <sup>3</sup> .....	M	26	25	Left occipital	110 Gm.; 7.5 by 8 cm. in roentgenogram	Headache, swelling in left occipital region	+	+	+	0
14. Bucy (case 1) 1934.....	M	28	5	Right parietal	1½ by 1¼ in.; elevated ¾ in.	Convulsion	+	Broken	+	Slight
15. Bucy (case 2) 1934.....	F	26	24	Left frontal	1½ by 1½ in.	Local swelling	+	Small	+	0
16. Bucy (case 3) 1934.....	M	39	Many years' duration	Midline frontal	2½ by 1½ in.; elevated 1 in.	Local swelling	+	Small	+	0

cases reported by both Körner<sup>8</sup> and Borchardt<sup>9</sup> the tumor was definitely stated to have arisen between the bone and the dura mater, not within the bone.

#### SUMMARY

Three cases of epidermoid tumor (cholesteatoma) arising within the diploe of the skull are reported. Such neoplasms are very rare, only thirteen having been recorded prior to the present report. These tumors, which arise from displaced anlagen of surface epithelium, expand the diploe and separate and erode the tables of the skull. The defect visible in the roentgenogram is typical of the condition. These intradiploic cholesteatomas rarely give rise to neurologic symptoms. The treatment is purely surgical. A permanent cure may be expected only if the tumor is completely removed.

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8. Körner, O.: Ein Cholesteatoma verum in der hinteren Schädelgrube durch eine acute Mittelohreiterung infiziert und vereitert: Operation. Heilung. Ztschr. f. Ohrenh. **37**:352, 1900.

9. Borchardt, M.: Cholesteatom der hinteren Schädelgrube, Arch. f. klin. Chir. **77**:892, 1905.

# ABERRANT PANCREATIC TISSUE IN THE GASTRO- INTESTINAL TRACT

A REPORT OF TWENTY-FOUR CASES

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The occurrence of aberrant pancreatic tissue, discovered either at operation or at autopsy, has been reported from time to time since the first case was described by Klob<sup>1</sup> in 1859. From that date until 1904, when Warthin<sup>2</sup> made the first comprehensive study of the literature, reports of isolated cases were published. Warthin collected forty-seven cases, to which he added two. Since then surveys of the literature have been made by Horgan<sup>3</sup> in 1921, by Simpson<sup>4</sup> in 1927 and by Hunt and Bonesteel<sup>5</sup> in 1934. The last review brought the total number of cases to one hundred and eighty-six. Since the completion of Hunt and Bonesteel's paper at least ten additional examples<sup>6</sup> have been reported, to which we are adding reports of twenty-four cases in which aberrant pancreatic tissue was found at various locations in the gastro-intestinal tract.

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From the Departments of Surgery and Pathology of the Peter Bent Brigham Hospital, the Children's Hospital and the Harvard Medical School.

1. Klob, J.: *Pancreas-Anomalien*, Ztschr. d. Gesellsch. d. Aerzte z. Wein **15**:732, 1859.

2. Warthin, A. S.: *Two Cases of Accessory Pancreas*, *Physician & Surg.* **26**:337, 1904.

3. Horgan, E. J.: *Accessory Pancreatic Tissue*, *Arch. Surg.* **2**:521 (May) 1921.

4. Simpson, W. M.: *Aberrant Pancreatic Tissue*, in *Contributions to Medicine and Surgery*, dedicated to Aldred Scott Warthin, Ann Arbor, Mich., George Wahr, 1927, p. 435.

5. Hunt, V. C., and Bonesteel, H. T. S.: *Meckel's Diverticulum Containing Aberrant Pancreas*, *Arch. Surg.* **38**:425 (March) 1934.

6. (a) Best, R. R., and Bowers, W. F.: *Anterior Hemipylorotomy for Aberrant Pancreatic Tissue of the Duodenum*, *Ann. Surg.* **99**:967, 1934. (b) King, E. S. J., and MacCallum, P.: *Pancreatic Tissue in the Wall of the Stomach*, *Arch. Surg.* **28**:125 (Jan.) 1934. (c) Okinczyk, J.: *Deux observations de pancréas aberrant*, *Bull. et mém. Soc. nat. de chir.* **58**:1427, 1932. (d) Puhl, H.: *Primäres Jejunalgeschwür mit heterotoper Fundusschleimhaut*, *Deutsche Ztschr. f. Chir.* **239**:624, 1933. (e) Wertheimer, P.: *Pancreas aberrant et gastrorrhagies*, *Bull. et mém. Soc. nat. de chir.* **59**:243, 1933.

In the cases previously reported the most common site for the aberrant pancreatic tissue was in the upper portion of the gastro-intestinal tract, and in almost 80 per cent of the cases the anomaly was found in the wall of the stomach, duodenum or jejunum. In the majority of the remaining cases the aberrant pancreatic substance was located in the ileum, appearing particularly in diverticula of that portion of the small intestine. A few cases have been described in which pancreatic tissue occurred outside of the gastro-intestinal tract; in one case it occurred in the omentum,<sup>2</sup> in one in the mesenteric fat,<sup>7</sup> in one in an umbilical fistula,<sup>8</sup> in two in the wall of the gallbladder,<sup>9</sup> and in three in the splenic capsule.<sup>10</sup> Thus it is seen that in most instances the anomalous location of these fragments is in part derived from the foregut.

No explanation universally accepted has been given for the origin of aberrant pancreatic tissue. Zenker<sup>11</sup> attributed it to the formation of an additional pancreatic bud from the foregut which developed as an independent glandular mass and which had been carried away from its point of origin as the gut elongated. Glinski<sup>12</sup> interpreted the presence of the anomaly as a failure of a primitive anlage, probably the ventral bud or a part of it, to coalesce with the dorsal portion. Warthin<sup>2</sup> expressed the belief that accessory pancreatic tissue was formed from the lateral budding of the rudimentary pancreatic ducts as they penetrated the intestinal wall and that the mass of pancreatic tissue thus formed was snared off and carried upward or downward by the longitudinal growth of the intestine. This theory has had the support of Simpson.<sup>4</sup> Horgan<sup>3</sup> stated that buds of the pancreatic anlage attached themselves to any organ with which they came in contact and were carried away by growth or change in position. Moore<sup>13</sup> offered the

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7. Thorel, C.: *Histologisches über Nebenpankreas*, Virchows Arch. f. path. Anat. **173**:281, 1903.

8. Wright, J. H.: *Aberrant Pancreas in the Region of the Umbilicus*, J. Boston Soc. M. Sc. **5**:497, 1901.

9. Cogniaux, P.: *Contribution à l'étude des pancréas aberrants*, Arch. franco-belges de chir. **31**:307, 1928. von Hedry, N.: *Nebenpankreas in der Gallenblasenwand*, Beitr. z. klin. Chir. **132**:570, 1924.

10. Ellis, A. G.: *Accessory Pancreas, with Report of Two Cases*, Proc. Path. Soc. Philadelphia **29**:25, 1908. Lubarsch, O.: *Ueber das Vorkommen von Pankreasläppchen in der Milz*, Virchows Arch. f. path. Anat. **254**:880, 1925. Weidman, F. D.: *Aberrant Pancreas in the Splenic Capsule*, Proc. Path. Soc. Philadelphia **31**:267, 1910.

11. Zenker, F. A.: *Nebenpankreas in der Darmwand*, Virchows Arch. f. path. Anat. **21**:369, 1861.

12. Glinski, L. K.: *Zur Kenntnis des Nebenpankreas und verwandter Zustände*, Virchows Arch. f. path. Anat. **165**:132, 1901.

13. Moore, R. A.: *Accessory Pancreases: Report of a Case with a Discussion of Their Pathology and Origin*, Am. J. Path. **5**:407, 1929.

explanation that adhesions may cut across the main pancreatic anlage and isolate portions which can subsequently be implanted elsewhere. Taylor,<sup>14</sup> in his work on heterotopias of the alimentary tract, quoted Mathias,<sup>15</sup> Beutler<sup>16</sup> and Delhougne<sup>17</sup> as holding that accessory pancreatic tissue represents an atavistic phenomenon and reproduces a condition normally seen in certain lower animals and fishes, in which the pancreas is not a single organ but is diffusely scattered through the peritoneum and muscular coats of the intestinal wall. Recently King and MacCallum<sup>18</sup> concluded that aberrant pancreatic tissue, which they had observed four times in the wall of the stomach, arose from the normal gastric epithelium under the action of abnormal stimuli. It was the thesis of these authors that the normal gastric mucosa undergoes a metaplasia to a pancreatic type of tissue when altered by chronic inflammatory changes.

Aberrant pancreatic tissue in the intestinal tract may apparently persist throughout life without producing clinical symptoms or pathologic changes, but occasionally it may give rise to one of several important lesions. This anomaly may act in a purely mechanical manner and cause either pyloric or intestinal obstruction. Such cases are reported by Albrecht and Artz,<sup>19</sup> Branham<sup>20</sup> and Hale.<sup>21</sup> Cases of intussusception wherein the pancreatic tissue has acted as the leading point have been reported by Benjamin,<sup>22</sup> Bize,<sup>23</sup> Brunner,<sup>24</sup> Hulst<sup>25</sup>

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14. Taylor, A. L.: *The Epithelial Heterotopias of the Alimentary Tract*, J. Path. & Bact. **30**:415, 1927.

15. Mathias, E.: *Die Abgrenzung einer neuen Gruppe von Geschwülsten*, Berl. klin. Wchnschr. **57**:444, 1920; *Zur Kasuistik seltener Geschwulstbildungen*, *ibid.*, p. 398.

16. Beutler, A.: *Ueber blastomatöses Wuchern von Pankreaskeimen in der Magenwand*, Virchows Arch. f. path. Anat. **232**:341, 1921.

17. Delhougne, H.: *Ueber Pankreaskeime im Magen*, Arch. f. klin. Chir. **129**:116, 1924.

18. Albrecht, H., and Artz, L.: *Beiträge zur Frage der Gewebsverirrung: II. Ueber die Bildung von dystrophischem Pankreas*, Frankfurt. Ztschr. f. Path. **4**:167, 1910.

19. Branham, J. H.: *Operative Treatment of Cancer of the Stomach, with Report of Six Partial Gastrectomies*, Maryland M. J. **51**:144, 1908.

20. Hale, K.: *Study of the Accessory Pancreas, with Report of One Causing Congenital Pyloric Stenosis*, Ann. Surg. **83**:774, 1926.

21. Benjamin, A. E.: *Accessory Pancreas with Intussusception*, Ann. Surg. **67**:293, 1918.

22. Bize: *Etude anatomo-clinique des pancréas accessoires situés à l'extrémité d'un diverticule intestinale*, Rev. d'orthop. **5**:149, 1904.

23. Brunner, C.: *Ein Beitrag zur Chirurgie und pathologischen Anatomie der Darminvagination*, Beitr. z. klin. Chir. **25**:344, 1899.

24. Hulst, J. P. L.: *Ueber einen in einem Darmdivertikel gelagerten Pankreaskeim mit sekundärer Invagination*, Centralbl. f. allg. Path. u. path. Anat. **20**:12, 1909.

and Taylor.<sup>14</sup> Nauwerck,<sup>25</sup> Newmann<sup>26</sup> and Simon<sup>27</sup> expressed the belief that some intestinal diverticula are formed because of the weakening of the musculature of the intestinal wall by the presence of the aberrant pancreatic tissue at this point. This explanation has been a favorite one in describing the origin of many duodenal diverticula.

An inflammatory reaction of considerable magnitude may arise in aberrant pancreatic tissue. The symptoms of ulcer of the pylorus or duodenum may be closely simulated by an ulcerative process in the aberrant pancreatic tissue located at one of these sites. The presence of pancreatic tissue in such ulcers leads one to suspect that the anomalous substance so alters the normal relationships of the parts, or so changes the blood supply to the regional mucosa, that ulceration is prone to occur where this anomaly exists. Of the various pathologic processes which may be caused by the abnormality, superficial ulceration is the most common. Best and Bowers,<sup>6a</sup> Cave,<sup>28</sup> Cafritz,<sup>29</sup> Cohen<sup>30</sup> and Deaver and Reimann<sup>31</sup> reported the occurrence of such changes. It is well to bear in mind the possibility of such a lesion in cases of peptic ulcer. Inflammatory reaction in aberrant pancreatic tissue of a Meckel diverticulum or of some other intestinal diverticulum may give rise to symptoms closely resembling those of appendicitis. There are two reports, one by Hunt and Bonesteel<sup>5</sup> and a second by Thomson,<sup>32</sup> which record the occurrence of symptoms simulating those of appendicitis; in each case the symptoms were due to the fact that there was ulceration of the pancreatic tissue at the tip of a Meckel diverticulum.

A more rare condition which merits consideration in a study of this anomaly is the possibility of malignant change in the pancreatic tissue. The location of the lesion when the nodule projects into the intestinal lumen presents an excellent opportunity for irritative action which may lead through inflammation of a chronic type to neoplastic changes.

25. Nauwerck, C.: *Ein Nebenpankreas*, Beitr. z. path. Anat. u. z. allg. Path. **12**:29, 1892.

26. Newmann, E.: *Nebenpankreas im Darmdivertikel*, Arch. d. Heilk. **11**:200, 1870.

27. Simon, H.: *Beitrag zur Kenntnis der abgesprengten Pankreaskeime*, Erlangen, E. T. Jacobs, 1905; quoted by Hunt and Bonesteel.<sup>5</sup>

28. Cave, H. W.: *Aberrant Pancreatic Tissue Simulating Duodenal Ulcer*, Am. J. Surg. **5**:537, 1928.

29. Cafritz, E. A.: *Accessory Pancreatic Tissue*, South. M. J. **22**:833, 1929.

30. Cohen, H.: *Accessory Pancreas with Ulcer of Pylorus*, Surg., Gynec. & Obst. **34**:384, 1922.

31. Deaver, J. B., and Reimann, S. P.: *Surgical Treatment and Pathology of Gastric and Duodenal Ulcer*, Surg., Gynec. & Obst. **32**:103, 1921.

32. Thomson, H. A.: *Diverticula of the Intestinal Tract*, Lancet **1**:860, 1908.



Instances of carcinomatous manifestations have been recorded by Branham,<sup>10</sup> Bookman<sup>33</sup> and Semsroth.<sup>34</sup>

These described lesions in aberrant pancreatic tissue are of interest to those dealing with the surgery and pathology of the gastro-intestinal tract. It is, however, no less important to recognize the nature of this anomalous tissue and to know that it may occur without giving rise to important changes. In the latter regard, it has been an unfortunate experience in several of our cases to mistake the tissue for a carcinomatous lesion of the stomach or intestine. The prolongation of the operation while removing benign pancreatic nodules and the danger of unnecessary opening of the intestine in these instances could have been obviated if the nature of the "nubbins" had been recognized at operation.

The following abstracts of twenty-four cases were collected from the records of the Boston Children's Hospital and the Peter Bent Brigham Hospital. These cases are summarized in the table.

#### REPORT OF CASES

CASE 1.—R. C., a girl aged 8 days, entered the hospital for treatment of a spina bifida and an infected meningocele. Death ensued from meningitis.

*Gross Pathologic Description.*—In the midportion of the jejunum there were two nodular masses lying within the wall of the intestine which projected into the lumen of the jejunum. The largest of these measured 4 mm. in diameter and was elevated to form a flattened projection 3 mm. in height. The mucosa covered this tissue, and there was no ulceration or evidence of inflammation in the area. The second nodule in the jejunum was approximately 3 mm. in diameter and 2 mm. in thickness and was covered by mucosa.

*Microscopic Examination.*—The "nubbins" of aberrant tissue lay wholly within the submucosa (fig. 1). This anomalous tissue had the general histologic picture of normal pancreatic tissue with regard to acinar structure, ductules and stroma, but islets of Langerhans cells were missing. There was no inflammatory reaction in the nodules. The mucosa over these masses was largely destroyed by post-mortem autolysis, but there was no regional evidence of inflammatory reaction.

CASE 2.—E. D., a girl aged 2 weeks, entered the hospital after an illness of twenty-four hours and died of bacteremia, bronchopneumonia, acute bronchitis and tracheitis.

*Gross Pathologic Description.*—Fifty centimeters above the ileocecal valve there was a Meckel diverticulum which measured 3.5 cm. in length. There was no inflammatory change of the mucosa lining the diverticulum. On the outer surface of the diverticulum, and covered by serosa, there was a thin, grayish-white, flat nodule about 0.5 cm. in diameter. This appeared to be accessory pancreatic tissue.

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33. Bookman, M. R.: Carcinoma of Duodenum Originating from Aberrant Pancreatic Cells, *Ann. Surg.* 95:464, 1932.

34. Semsroth, K.: Histologic Interpretation of Certain Carcinoids of Small Intestines; Neoplasm-Like Malformation of Tissue of Pancreas, *Arch. Path.* 6:575 (Oct.) 1928.

*Microscopic Examination.*—The mucosa of the diverticulum resembled the type of mucosa found in the small intestine, but there was no distinct muscularis mucosae. The submucosa was represented by only a few strands of connective tissue.

*Summary of Cases of Aberrant Pancreatic Tissue Occurring in the Gastro-Intestinal Tract*

Case	Age	Sex	Location of Aberrant Pancreatic Tissue	Size of Mass of Aberrant Pancreatic Tissue	Pathologic Change	Pancreatic Tissue Found at
1	8 days	F	Jejunum (2 nodules)	4 mm. diameter 3 mm. diameter	None	Autopsy
2	2 weeks	F	Meckel diverticulum	5 mm. diameter	None	Autopsy
3	4 weeks	F	Pyloric ring	3 mm. diameter 2 mm. thickness	None	Autopsy
4	7 weeks	M	Meckel diverticulum	8 mm. diameter	None	Autopsy
5	3 months	M	Jejunum	7 mm. diameter 4 mm. thickness	None	Autopsy
6	3 months	M	Ilium	1 cm. diameter 4 mm. thickness	None	Autopsy
7	10 months	M	Duodenum	1.2 cm. diameter	Ulcer with hemorrhage	Autopsy
8	1 year	F	Meckel diverticulum	1.5 cm. diameter 6 mm. thickness	None	Autopsy
9	3 years	M	Duodenum	7 mm. diameter 4 mm. thickness	None	Autopsy
10	4 years	F	Meckel diverticulum	6 mm. diameter 2 mm. thickness	None	Operation
11	7 years	F	Meckel diverticulum	5 mm. diameter 3 mm. thickness	None	Autopsy
12	9 years	M	Meckel diverticulum	5 mm. diameter 3 mm. thickness	None	Autopsy
13	11 years	F	Jejunum	8 mm. diameter 4 mm. thickness	None	Autopsy
14	33 years	M	Duodenum	1.3 cm. diameter 5 mm. thickness	None	Autopsy
15	50 years	M	Duodenum	7 mm. diameter 4 mm. thickness	None	Autopsy
16	54 years	F	Stomach	Many "nubbins" 2-4 mm. diameter	Ulcer	Operation
17	58 years	F	Duodenum	2 cm. diameter 6 mm. thickness	None	Operation
18	58 years	M	Duodenum	5 mm. diameter 3 mm. thickness	None	Operation
19	58 years	M	Duodenum	1 cm. diameter 3 mm. thickness	None	Autopsy
20	60 years	M	Jejunum	3 by 2 cm. 5 mm. thickness	None	Autopsy
21	65 years	F	Duodenum	1.5 cm. diameter 7 mm. thickness	Ulcer with hemorrhage	Autopsy
22	66 years	F	Pylorus	Spherical 1 cm. diameter	Obstruction of pylorus	Operation
23	69 years	M	Duodenum	7 nodules 1-9 mm. diameter	None	Autopsy
24	82 years	F	Duodenal diverticulum	Capped diverticulum	None	Autopsy

External to the musculature there was a flattened "nubbin" of pancreatic tissue which was covered by serosa (fig. 2). This aberrant substance was histologically the same as normal pancreas, except for the fact that no islets of the Langerhans type were present. The ducts were small and not dilated. They were lined by a cuboidal type of epithelium. There was no communication between these structures and the lumen of the diverticulum in the sections studied. There was no inflammatory or cicatricial process in any part of the diverticulum.

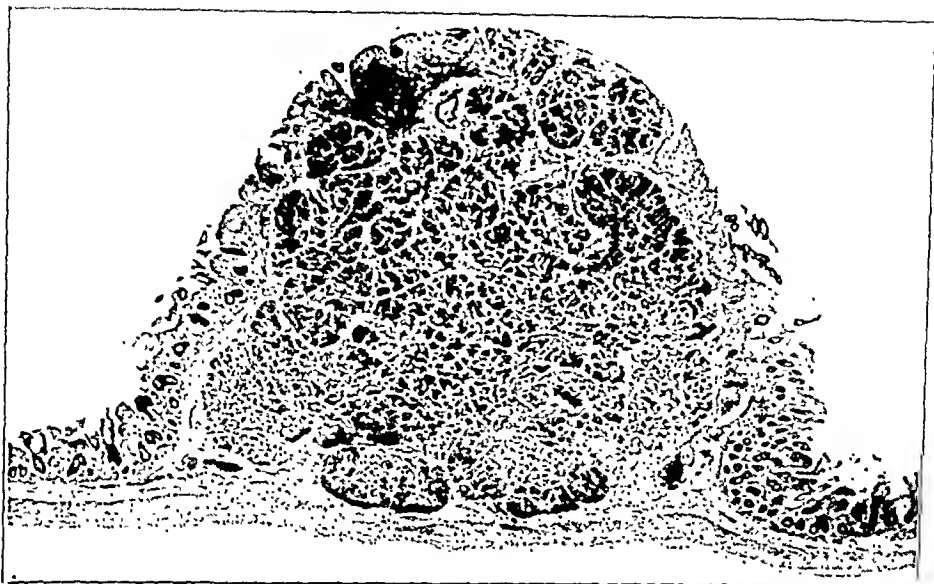


Fig. 1 (case 1).—Photomicrograph ( $\times 15$ ) of aberrant pancreatic tissue occurring in the wall of the jejunum. The pancreatic substance is covered internally by mucosa and externally by intestinal muscularis.

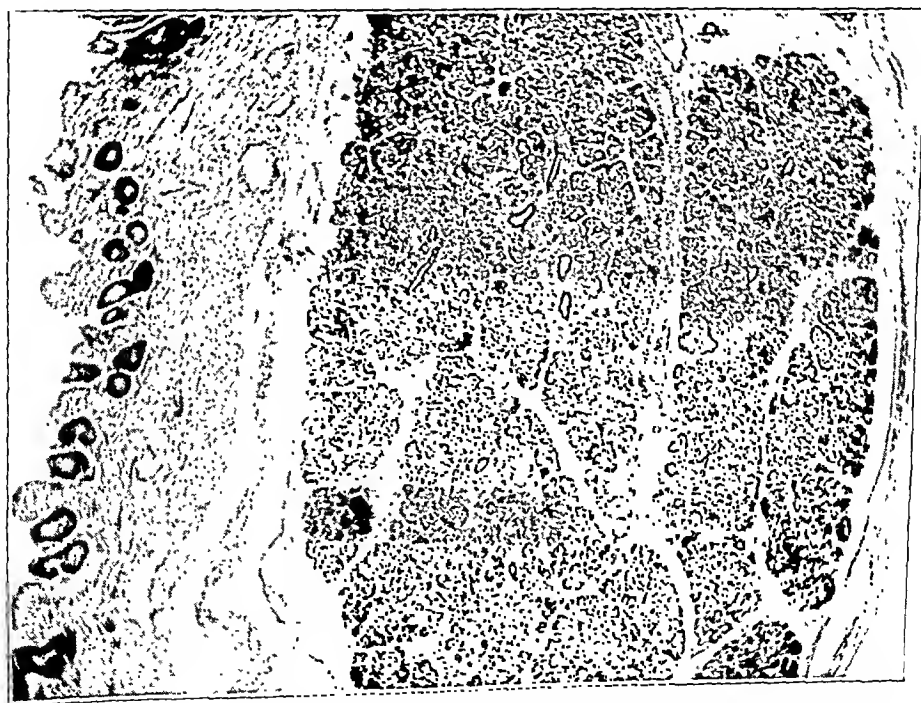


Fig. 2 (case 2).—Photomicrograph ( $\times 20$ ) of pancreatic tissue occurring in the wall of a Meckel diverticulum.

CASE 3.—E. B., a girl aged 1 month, entered the hospital on Sept. 26, 1926, because of difficulty in breathing of one day's duration. The results of physical examination and the clinical course indicated congenital cardiac disease. The patient died three days after admission.

*Gross Pathologic Description.*—Just at the pylorus a small mass was felt in the wall at the superior border of the pyloric ring. Proximal to the ring along the lesser curvature of the stomach was an elevation of the mucosa about 2 mm. in height and 3 mm. in diameter. This resembled a small nipple and at its tip presented a small mouth about 1 mm. in diameter. In the wall of the stomach beneath the site of this projection there was a nodule 8 mm. in diameter. When this was sectioned a glistening, pearly white surface was exposed.

*Microscopic Examination.*—Lying almost entirely within the muscularis of the pylorus there were islands of pancreatic tissue which were separated from one another by intervening bundles of the smooth musculature. This aberrant substance consisted of pancreatic acinar cells grouped into small lobules and intermixed with a few small ducts lined by cuboidal cells. There were no islets of the Langerhans type. The ducts of this nodule connected with larger ducts coursing out in the submucosa. The latter ducts were lined by columnar cells and apparently communicated with the intestinal lumen.

CASE 4.—C. H., a boy aged 7 weeks, entered the hospital for treatment of cellulitis of the face, abdomen and thigh. He died nine days later. The past history had been essentially irrelevant, and there had been no evidence of gastrointestinal abnormality.

*Gross Pathologic Description.*—In the terminal ileum there was a Meckel diverticulum measuring 2 cm. in length. At its tip there was a spherical mass of rather firm tissue 8 mm. in diameter. There was no evidence of ulceration or inflammatory change within the mucosa of the diverticulum.

*Microscopic Examination.*—The aberrant pancreatic tissue was situated within the submucosa and divided the muscularis into separate bands. It was covered on its inner aspect by normal mucosa of the type found in the ileum and on the outer surface by a thin serosa. The general appearance of the tissue resembled that of normal pancreatic acinar substance, except that it was divided into lobules by the bands of smooth muscle. In addition, there were large dilated ducts, having an almost acinar form, which were lined by columnar epithelium. There were no cells of the Langerhans islet type. The stroma was scanty, and there was no inflammatory reaction.

CASE 5.—Q. V., a boy aged 3 months, entered the hospital on July 3, 1922, because of jaundice of one week's duration. The clinical diagnosis was jaundice, secondary to generalized sepsis. Death ensued three days later.

*Gross Pathologic Description.*—In the jejunum there was a firm, gray, flattened nodule beneath the visceral peritoneum. This measured approximately 0.7 cm. in diameter and 4 mm. in thickness.

*Microscopic Examination.*—The nodule almost completely replaced the musculature but was pierced in a few places by small bundles of the circular fibers. The aberrant tissue consisted of a compact structure with general histologic features closely resembling those of normal pancreatic tissue except for the absence of islets. The acinar structures were supplied by a few small ducts. The nodule was covered on a portion of its external surface by some fibers of longitudinal intestinal musculature, but for the most part it was covered only by a thin serosa. The mass projected up to the muscularis mucosae but did not extend into the

mucosa. The intestinal mucosa over the nodule was intact and showed no inflammatory change, ulceration or scarring. There was no inflammatory reaction in the pancreatic substance.

CASE 6.—J. J. T., a boy aged 3 months, entered the hospital on Sept. 15, 1923, because of persistent diarrhea, vomiting and drowsiness of three days' duration. Bronchopneumonia and bilateral otitis media developed, and the child died fourteen days later.

*Gross Pathologic Description.*—In the first portion of the ileum, a "nubbin" was found in the intestinal wall. This was 1 cm. in diameter and 0.4 cm. in thickness. It lay on the antimesenteric side of the intestine. It was firm, slightly grayish and finely lobulated.

*Microscopic Examination.*—The nodule partially replaced the musculature but was pierced in a few places by fine strands of the intestinal muscularis. Only the serosa covered the outer surface. The inner border extended up to the muscularis mucosae. The overlying intestinal mucosa showed no important variation from the normal. The pancreatic tissue had the general histologic structure of normal pancreatic tissue except for the few intervening muscle fibers and the absence of Langerhans islets. The general arrangement of acinar cells and the form of the ducts resembled the respective features of normal pancreatic tissue. Secretory material could be seen in the ducts. There was no opening of the ducts to the intestinal lumen in the sections studied. There was no inflammatory reaction or scarring.

CASE 7.—E. A., a boy aged 10 months, was admitted to the hospital on Feb. 10, 1917, for treatment of a postauricular abscess. Subsequently bronchopneumonia and pleuritis developed, and the patient died sixteen days later. No intestinal abnormality was suspected.

*Gross Pathologic Description.*—The duodenum was filled with a reddish-black friable blood clot. On the superior wall of the duodenum and about 1 cm. below the pylorus there was an area of reddening and ulceration 1 cm. in diameter. The base of this was granular and mottled. The margins and base of this area of ulceration were not indurated, but they were slightly elevated. At the base of the aforementioned area and presenting on the serosal surface of the duodenum, there was a firm, flattened nodule 1.2 cm. in diameter and 4 mm. in thickness. The external surface of this nodule was pinkish gray and finely lobulated. Partially changed blood was present throughout the entire intestinal tract.

*Microscopic Examination.*—The muscularis was intact throughout the section and maintained a normal uninterrupted double-layered form. About half of the aberrant pancreatic tissue lay outside of the muscularis and was covered by serosa. The remaining half lay inside of the muscularis and extended up to the Brunner glands of the duodenum. The histologic structure of the aberrant tissue resembled that of normal pancreatic tissue with respect to the arrangement of acinar cells, amount of stroma, distribution of ducts and presence of Langerhans islets. External to the muscularis there was no inflammatory process, but inside of the muscle layer there was an acute necrosis of pancreatic tissue, intestinal submucosa and mucosa with evidence of hemorrhage, ulceration and deposition of fibrinoid material. The area was moderately infiltrated with polymorphonuclear leukocytes. There was no evidence of organization. There was no scarring indicative of old healed ulceration or inflammatory process.

CASE 8.—B. J. W., a girl aged 1 year, had a history of having had a respiratory infection for twelve days, followed by convulsions and fever. She died twelve hours after admission.

*Gross Pathologic Description.*—A Meckel diverticulum, 2 cm. in length, was found 75 cm. above the ileocecal valve. In the wall of the diverticulum there was a pinkish-gray nodule which measured 1.5 cm. in diameter and 0.6 cm. in thickness. On section it had a lobular structure and appeared to be accessory pancreatic tissue. The mucosa of the diverticulum showed no inflammatory change.

*Microscopic Examination.*—The mucosa of the diverticulum was essentially gastric in type, and large numbers of parietal cells were seen intermixed with the chief cell type. A portion of the mucosal lining resembled that of the ileum. The mucosa in some areas was thrown into prominent folds; elsewhere it was flattened and the glandular elements were missing. On one side of the wall of the diverticulum was the previously described nodule of pancreatic tissue. This lay wholly outside of the muscularis and was covered by serosa (fig. 3). This tissue closely

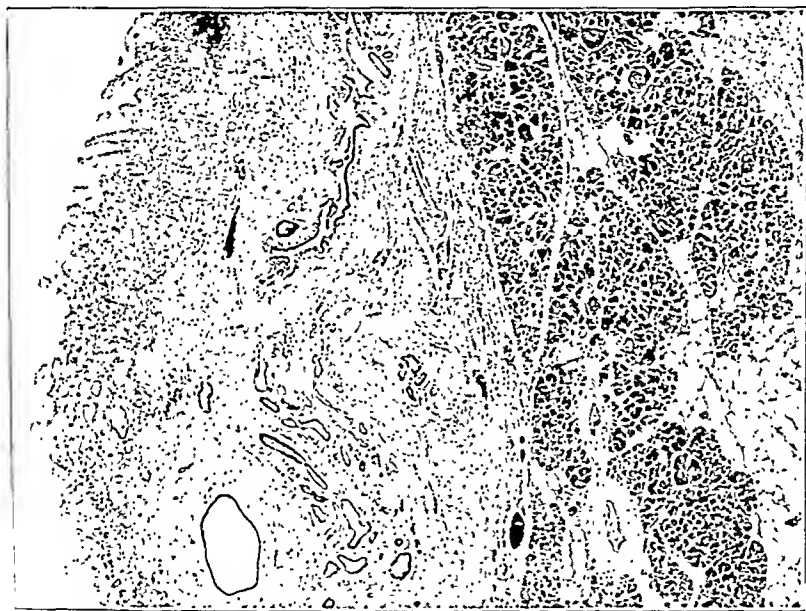


Fig. 3 (case 8).—Photomicrograph ( $\times 15$ ) of pancreatic substance occurring in the wall of a Meckel diverticulum. Toward the right there is acinar tissue scattered through which are several Langerhans islets. In the central portion of the photomicrograph are irregular ducts of varying size, many of which are dilated. The lumen of the diverticulum is toward the left.

resembled normal pancreatic substance in regard to general arrangement of acinar tissue, islet structures, ducts and stroma. The Langerhans islets were rather numerous.

CASE 9—L. F., a boy aged 3 years, entered the hospital on Oct. 19, 1917, for treatment of pneumonia and died the same day.

*Gross Pathologic Description.*—In the wall of the duodenum was a nodule 7 mm. in diameter and 4 mm. in thickness. This was firm and finely lobulated; the inner surface was covered by mucosa; externally the nodule was covered by serosa. The "nubbin" imparted a light grayish color to the intestinal epithelium and serosa.

*Microscopic Examination.*—The major part of the aberrant tissue lay between the muscularis and the Brunner's glands. There was, in addition, a thin layer of pancreatic substance between the intact muscularis and the serosa. The tissue resembled that of normal pancreas in all respects. There were many islets of Langerhans cells (fig. 4). There were no inflammatory changes or scarring. The overlying mucosa was normal.

CASE 10.—C. C., a girl aged 4 years, entered the hospital on Feb. 20, 1930. She had been ill for four days with what proved to be appendicitis with perforation. At operation a gangrenous appendix was removed and a Meckel diverticulum was resected. The patient was discharged as cured on March 24.

*Gross Pathologic Description.*—The Meckel diverticulum measured 3 cm. in length and 1 cm. in diameter. The entire diverticulum was diffusely hemorrhagic

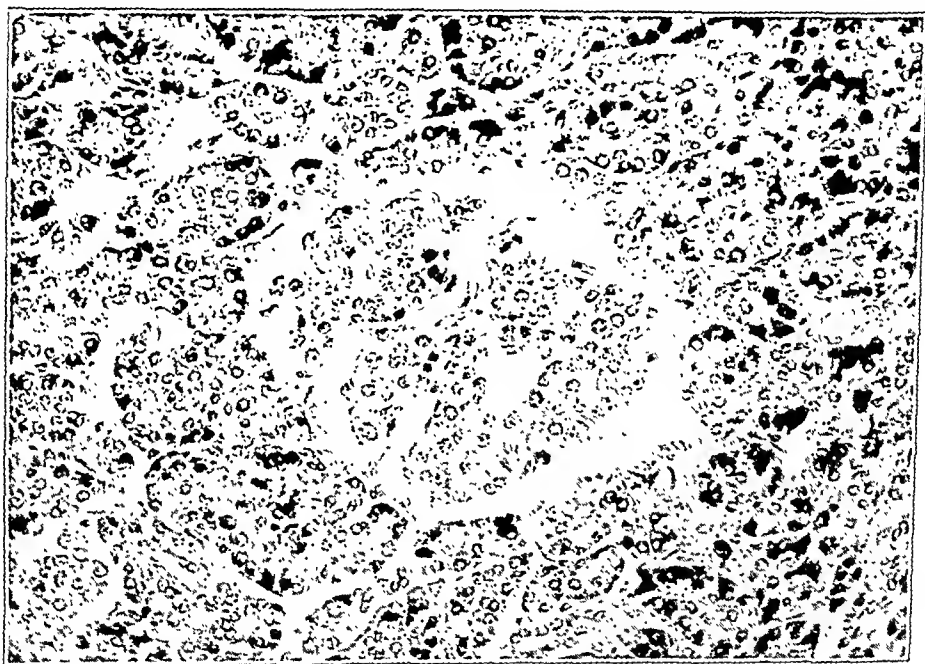


Fig. 4 (case 9).—Photomicrograph ( $\times 200$ ) of pancreatic tissue occurring in the wall of the duodenum, showing normal acinar structures and an islet of Langerhans.

and congested. At the apex of the diverticulum there was a small rounded lesion 6 mm. in diameter and 2 mm. in thickness which apparently lay within the sub-mucosal layer. The mucosa over this was intact and showed no ulceration. This nodule was pinkish gray and firm and on cross-section had a faint lobular appearance.

*Microscopic Examination.*—The mucosa of the diverticulum was entirely of the type found in the ileum. Within the muscularis there was a nodule of aberrant tissue which had the histologic structure of normal pancreatic tissue except for the absence of islets of Langerhans cells. The number and size of ducts, arrangement of acini and amount of stroma were of the proportion seen in the normal pancreas. There was no inflammatory reaction within the nodule of pancreatic tissue, but on the serosal surface of the diverticulum there was an acute fibrino-

hemorrhagic and purulent exudate indicative of peritonitis (secondary to ruptured appendicitis). The mucosa was intact in the nodule and showed no ulceration or scarring.

CASE 11.—P. J., a girl aged 7 years, entered the hospital on Nov. 27, 1931, after an illness of one week which proved to be meningitis. Laboratory studies showed the causative organism to be a pneumococcus. The patient died four days after entry.

*Gross Pathologic Description.*—A Meckel diverticulum was found 1 meter above the ileocecal valve. It was approximately 4 cm. in length and 1.5 cm. in diameter. On one side of the diverticulum was a small, flattened "nubbin" 5 mm. in diameter and 3 mm. in thickness. This was pinkish gray and was covered by serosa. The mucosa of the diverticulum was intact and showed no ulceration or scarring.

*Microscopic Examination.*—In the wall and scattered through the muscularis and beneath the serosa of the diverticulum there was a small mass of tissue which had the histologic structure of normal pancreatic tissue except that there were no Langerhans islets. There was no inflammatory reaction in this pancreatic tissue. The mucosa of the diverticulum was gastric in type.

CASE 12.—H. M., a boy aged 9 years, entered the hospital on Aug. 29, 1931, and died on September 2. For four days before admission the patient had symptoms suggestive of meningitis. The course while he was in the hospital and the findings showed an influenzal meningitis. The past history was entirely irrelevant. There had been no previous symptoms referable to the gastro-intestinal tract.

*Gross Pathologic Description.*—Routine examination disclosed a Meckel diverticulum about 1.5 meters proximal to the ileocecal valve. The Meckel diverticulum was 3 cm. long and 1.5 cm. in diameter. The mucosa was smooth. The serosal surface was also smooth and unbroken except at the tip of the diverticulum where there was a small "nubbin" of tissue 5 mm. in diameter and 3 mm. in thickness beneath the serosa. The cut surface of this nodule had a faint lobulation and was pale pinkish gray.

*Microscopic Examination.*—The epithelium of most of the diverticulum was similar to that normally found in the ileum. The mucosal epithelium overlying the aberrant tissue was gastric in type and contained many parietal cells. Lying within the muscularis of the diverticulum (which elsewhere consisted of two layers) there was pancreatic tissue which was divided into lobules by bundles of the muscular layer. The external surface was covered by serosa. The pancreatic substance consisted of intermixed acinar tissue and ducts of varying size. The epithelium of the duct was mostly cuboidal, but a small portion was low columnar. Some of the ducts were dilated. Several ducts passed up through the mucosa and connected with the lumen of the diverticulum by way of the gastric glands. The acinar tissue was similar in appearance to that found in normal pancreatic tissue. There were no islets of Langerhans cells. The stroma was moderately dense. There was no inflammatory reaction.

CASE 13.—H. D., a girl, aged 11 years, entered the hospital on Oct. 24, 1929, after an illness of one week which proved to be miliary tuberculosis and tuberculous meningitis.

*Gross Pathologic Description.*—In the upper portion of the jejunum there was a small nodule within the intestinal wall which was approximately 8 mm. in diameter and 4 mm. in thickness. This was covered by mucosa, and the surface was not ulcerated. The tissue was grayish pink and firm and had a faint lobular appearance on cross-section.



*Microscopic Examination.*—The aberrant pancreatic tissue lay entirely within the submucosa. The mucosa was intact over the nodule and did not show any inflammatory reaction or ulceration. The pancreatic substance resembled normal pancreatic tissue except for the absence of islets of Langerhans cells. The acinar structures had the usual lobular arrangement. The smaller ducts were lined by cuboidal epithelium. A few of the larger ducts were dilated and were lined by a columnar epithelium.

CASE 14.—J. M., a man aged 33, was admitted to the hospital on June 9, 1928, with the complaint of abdominal pain and distention of three weeks' duration. A diagnosis of subacute bacterial endocarditis due to *Streptococcus viridans* was made. The patient's condition rapidly became worse, and he died on June 15.

*Gross Pathologic Description.*—A mass projecting on the external surface of the intestine was found on the anterior wall of the first part of the duodenum. This mass was 1.3 cm. in diameter and 0.5 cm. in thickness. It was light gray, was slightly lobulated and grossly resembled pancreatic tissue. It was entirely covered by serosa. The mass did not project into the intestinal lumen but could be seen beneath the normal-appearing, nonulcerated mucosa.

*Microscopic Examination.*—The nodule of aberrant tissue lay partially within the submucosa but mostly within the muscular layer of the intestine. The fibers of the muscularis were separated and coursed as isolated bundles through the pancreatic tissue. The mucosa was intact over the area, and the serosa was unbroken. The aberrant tissue consisted partially of a dense fibrous stroma in which there were many isolated ducts of varying size. The smaller ones were lined by cuboidal epithelium, and the larger ones, by columnar epithelium. In one small area there were glands of the Brunner type which merged into and connected with the ductal system. Scattered between the ducts were islands of pancreatic acinar tissue which had the general appearance of normal pancreatic substance. A small number of islets of the Langerhans type were seen. A few lymphoid cells were scattered through the stroma, but there was no active inflammatory process.

CASE 15.—M. B., a man aged 50, entered the hospital on March 25, 1932, because of cerebral hemorrhage. In spite of repeated removal of spinal fluid by lumbar puncture the patient's condition did not improve, and death occurred twenty-five days after admission.

*Gross Pathologic Description.*—In the wall of the duodenum a small, slightly raised nodule was found beneath the mucosal surface. This was 7 mm. in diameter and 4 mm. in maximum thickness. It was slightly lobulated, firm and pinkish gray. There was no ulceration of the overlying mucosa.

*Microscopic Examination.*—The aberrant pancreatic tissue lay entirely between the mucosa and the muscularis and almost completely replaced the Brunner glands in this area. There was no distinct muscularis mucosae; hence the pancreatic tissue abutted against the bases of the mucosal glands. Most of the tissue resembled closely the lobular, acinar structure of normal pancreatic tissue. A few normal-appearing islets of the Langerhans type were found. For the most part the stroma was of the same prominence as that found in normal pancreatic tissue, but in one deep area there was a dense stroma through which coursed numerous small ducts unaccompanied by acinar or islet elements.

CASE 16.—H. C., a woman aged 54, was admitted to the hospital on March 16, 1930, because of irregular vaginal bleeding of six months' duration. The past history was entirely irrelevant. A diagnosis of adenocarcinoma of the fundus was made; this was substantiated by microscopic examination of curetted material. On

March 17, 1930, a hysterectomy was performed by Dr. John Homans. Examination of the upper portion of the abdomen revealed a slightly umbilicated mass 1.5 cm. in diameter and 1 cm. in depth in the anterior surface of the gastric wall just proximal to the pylorus. This was thought to be a carcinoma in an early stage of development, and resection of this portion of the stomach was carried out. The patient's postoperative course was not remarkable.

*Gross Pathologic Description.*—At the line of junction between the duodenal and the gastric mucosa there was an ulcer which measured 1 cm. in diameter and 5 mm. in depth. It was sharply punched out and had well defined borders. Surrounding the ulcer there was cicatrization of the gastric wall in a zone varying from 5 to 10 mm. in width. Around the margin of the ulcer the mucosa was grayish pink and presented numerous small grayish-white elevations distinctly different in appearance from the surrounding mucosa. These elevations were firm and measured about 2 mm. in diameter. They were elevated 2 mm. above the surface of the surrounding mucosa.

*Microscopic Examination.*—In the gastric submucosa and extending down through the musculature there were islands of pancreatic tissue which were from 1 to 4 mm. in greatest dimensions. Bundles of gastric musculature coursed between the lobules of pancreatic substance. Smooth musculature and serosa covered the exterior of these nodules. This aberrant tissue had the appearance of normal pancreatic parenchyma. It consisted mostly of normal sized acini in lobular arrangements and was supported by a fine fibrous stroma. Small ducts coursed through this tissue. These were within the range of number and size found in normal pancreatic tissue. They were all lined by a cuboidal epithelium. A few islets of Langerhans were found. Extending along the external surface of the nodules was a layer about 2 mm. in thickness in which there were numerous ducts which were set in a dense stroma. These ducts, which were not accompanied by any cells of the acinar or islet type, varied greatly in size, some having a barely discernible lumen and others being large and dilated (fig. 5). Gradations in size between these two extremes were seen. Most of the epithelium was cuboidal, but in the larger ducts columnar epithelium was frequently seen. Slight scarring had replaced some of the pancreatic tissue, but in view of the adjacent ulceration the area was surprisingly free from any active inflammatory reaction. Small accumulations of lymphoid cells and occasional lymphoid germinal follicles were seen beneath the mucosal glands.

CASE 17.—D. Y., a Negress aged 58, entered the hospital on April 28, 1933, complaining of epigastric pain of three years' duration. For three months before admission the patient had vomited daily, and she had passed black stools during the same period. The patient became gradually weaker and lost 35 pounds (15.9 Kg.) in weight. Physical examination showed a well developed but poorly nourished Negress in some distress. Except for slight tenderness in the epigastrium the examination gave no remarkable results. Roentgen studies of the stomach showed an irregularity and narrowing of the distal 4 cm. of the antrum; this was interpreted as representing a carcinoma. Routine studies of the blood and urine gave normal results. Gastric analysis showed free hydrochloric acid equivalent to 43 cc., and total acidity equivalent to 64 cc., of tenth-normal sodium hydroxide. All specimens of gastric contents gave positive reactions to the benzidine test. The Wassermann and Hinton tests of the blood were negative.

*Operation.*—On April 29, 1933, Dr. Elliott C. Cutler resected the antral portion of the stomach for carcinoma.

*Gross Pathologic Description.*—The surgical specimen consisted of the antral end of the stomach, the pylorus and the first part of the duodenum. On the greater gastric curvature there was a neoplasm which later proved to be an adenocarcinoma. On the posterior wall of the first portion of the duodenum there was a rounded, raised nodule presenting on the outer surface of the intestine. This was 2 cm. in diameter and 6 mm. in thickness. It was covered by serosa. This tissue was slightly lobulated, was pinkish gray, and on cross-section had the general appearance of pancreatic tissue.

*Microscopic Examination.*—The aberrant pancreatic tissue lay almost wholly outside of the intestinal musculature, but a few small islands of this tissue were found between the muscle bundles. The outer surface of the specimen was covered by a normal serosa. The pancreatic tissue had essentially the same histologic fea-



Fig. 5 (case 16).—Photomicrograph ( $\times 12$ ) of an aberrant nodule occurring in the wall of the stomach, illustrating anomalous ducts of variable size lying within the submucosa. (Other areas in the same specimen showed typical acinar and islet tissue.)

tures as those found in normal pancreas. There was the usual arrangement of acinar and islet substance. The smaller ducts connected with larger ones, lined with columnar tissue, which emptied into the intestinal lumen. The mucosal epithelium and Brunner's glands showed no evidence of inflammatory reaction or cicatrization.

CASE 18.—J. S., a man aged 58, entered the hospital in November 1932 with the complaint of periodic vomiting of one year's duration. Two years before admission mild distention after meals began to develop; this became progressively worse until the time of hospitalization. There was no history of hematemesis. During the present illness the patient lost 15 pounds (6.8 Kg.). Physical examination showed him to be well developed and fairly well nourished. He vomited

several times during the examination. Except for a slight enlargement of the liver, the physical examination gave negative results. Roentgen studies of the gastrointestinal tract showed that the stomach was low, dilated and atonic. There was an irregularity involving the pyloric sphincter, and no barium sulphate was seen to pass from the stomach during examination. The findings indicated an obstructive lesion of the pylorus which was thought to be a carcinoma.

*Operation.*—On Nov. 5, 1923, Dr. David Cheever resected the antral portion of the stomach because of an extensive adenocarcinoma. At the time of operation a rounded mass of white tissue 5 mm. in diameter was discovered beneath the serosa on the anterior surface of the second part of the duodenum. This was thought to be a metastasis from the gastric carcinoma, and hence a portion of the duodenum was excised.

*Gross Pathologic Description.*—The first specimen consisted of the resected portion of the stomach and included the carcinoma. The second specimen consisted of a portion of duodenal wall which was about 1.5 cm. in diameter. In the center of this was a small rounded, flattened nodule about 5 mm. in diameter and about 3 mm. in thickness which was situated within the muscular layer of the intestinal wall. It was completely covered on its inner surface by mucosa and on its external surface by serosa. The nodule was slightly lobulated, firm but not hard and pinkish white.

*Microscopic Examination.*—The nodule lay totally within the duodenal musculature, which was expanded to surround it. Muscle bundles also coursed through the nodule in a trabecular arrangement, breaking the nodule into isolated islands. The serosa, submucosa and mucosa were normal and intact. The islands of aberrant tissue consisted largely of groups of ducts of varying type. Some of these were lined by tall columnar epithelium; others were lined by cuboidal epithelium. The ducts were relatively small, and no material was present in their lumens. These ducts did not communicate with the intestinal lumen in the sections studied. Some of the islands in the aberrant tissue consisted largely or wholly of cells in acinar arrangement and similar in appearance to normal pancreatic acinar substance. There were no tissues similar to islets of Langerhans cells. There was no inflammatory reaction in the nodule.

CASE 19.—S. H., a man aged 58, entered the hospital on Jan. 23, 1934, complaining of weakness of eight weeks' duration. There was a history of gradual swelling of the lymph glands of the right side of the neck for the past three years. The patient's condition became progressively worse, and death occurred on Feb. 3, 1934.

*Gross Pathologic Description.*—Autopsy disclosed a lymphoblastoma of the Hodgkins type with infiltrations of the spleen, liver, kidneys, abdominal and cervical lymph nodes and bone marrow. On the medial surface of the duodenum, 5 cm. below the pylorus, there was a nodule 1 cm. in diameter which was rough, rather firm, well defined and raised 3 mm. above the surrounding duodenal mucosa. The nodule was covered by normal-appearing mucosa.

*Microscopic Examination.*—There was no ulceration or inflammatory change of the mucosa or duodenal wall. Within the submucosa there was pancreatic tissue which largely replaced the Brunner glands in this area. These pancreatic cells were mostly of acinar type and typical in arrangement. There were also a few islets of the Langerhans type. The connective tissue stroma between the pancreatic lobules was fairly prominent.

CASE 20.—B. P., a man aged 60, was admitted to the hospital with the complaint of abdominal pain of three weeks' duration. Two weeks before admission

he began to suffer from loss of appetite and a continuous dull ache in the right lower quadrant of the abdomen. Physical examination revealed a slightly emaciated, icteric man. The liver was enlarged, and there was tenderness in the epigastric region. Otherwise the examination gave negative results.

*Operation.*—An exploratory laparotomy was performed. Thin bloody fluid was found within the abdominal cavity. Biopsy of hepatic tissue showed carcinoma without a demonstrable primary focus. The patient died on the sixth postoperative day.

*Gross Pathologic Description.*—Autopsy showed a carcinoma of the kidney with metastases to the lungs and liver. In the first part of the jejunum beneath the peritoneum there was a firm, white to pinkish-gray plaque surrounding about one third of the circumference of the intestine. This plaque measured 3 by 2 cm. and was 0.5 cm. in thickness. On incision it appeared to lie between the mucosa and the muscularis. It was lobular and had the general appearance of normal pancreatic tissue.

*Microscopic Examination.*—The sections showed inclusion of pancreatic tissue in the wall of the jejunum. This aberrant tissue lay in the submucosa and also between the muscle bundles. The inner surface of the intestine was entirely covered by mucosa, and the external surface was completely covered by a layer of muscle and serosa. The pancreatic substance consisted of groups of acinar cells arranged in lobules and reproducing essentially the structure of normal pancreatic tissue. No islets of Langerhans were seen. There were a few intermixed ducts. The larger ones were lined by tall columnar epithelium; the smaller ones showed a cuboidal type of epithelium. No ducts were seen emptying into the intestinal lumen. The stroma was prominent in some areas, and a few lymphocytes were found in this supporting tissue. There was no evidence of ulceration or inflammatory reaction in the overlying mucosa.

CASE 21.—E. N., a woman aged 65, came to the hospital on Oct. 23, 1929, because of weakness and loss of weight of several years' duration. For the preceding three months the patient's appetite had been poor. There had been repeated attacks of vomiting, an attack occurring after almost every meal.

The results of physical examination were not remarkable except for consolidation in the upper lobe of the right lung and evidence of loss of weight. Laboratory findings showed the number of red cells to be 4,200,000, the hemoglobin, 75 per cent, and the number of white cells, 30,000. The urine was normal. Examination of the stool disclosed a 4+ reaction to the benzidine and guaiac tests.

The patient became gradually weaker and more cyanotic. Death occurred on Oct. 28, 1929.

*Gross Pathologic Description.*—There was evidence of bilateral lobar pneumonia which was the immediate cause of death. On the anterior wall of the first portion of the duodenum, 3 cm. distal to the pyloric ring, there was an elevated, white nodular mass, measuring 1.5 cm. in diameter and 7 mm. in thickness. This was firm but not hard. Its internal surface supported a fibrinous blood clot; when this was removed an indurated ulcer 1 cm. in diameter with well defined edges was seen. The surface ulceration was the site of the intestinal bleeding. There was changed blood along the intestinal tract below this site. The other results of the autopsy were of secondary importance.

*Microscopic Examination.*—Section of the duodenal ulcer showed aberrant pancreatic tissue which was not continuous with the normal pancreas. This aberrant tissue completely replaced the intestinal glands and the Brunner glands and pene-

trated the entire duodenal wall to present on the serosal surface of the duodenum (fig. 6). The circular and longitudinal muscle of the duodenum coursed in isolated strands through the pancreatic tissue. This pancreatic substance was composed entirely of acinar cells in normal lobulations. Small ducts with cuboidal epithelium were scattered through the tissue. No islets of the Langerhans type were present. Through the pancreatic substance there was a mild infiltration of lymphocytes, of polymorphonuclear leukocytes and especially of endothelial leukocytes. This leukocytic reaction was almost entirely limited to the tissue just below the surface facing the intestinal lumen. Toward the intestinal lumen there was a hemorrhagic necrosis of acinar tissue, and on the surface of the pancreatic tissue there was a fibrinohemorrhagic exudate. A small artery was found eroded in the base of the ulceration. This contained an unorganized fibrinous thrombus and was obviously the site of the intestinal bleeding. Chronicity of the ulcerative process was indicated by a moderate fibroblastic proliferation and fibrosis between the acini just beneath the surface of the lumen.

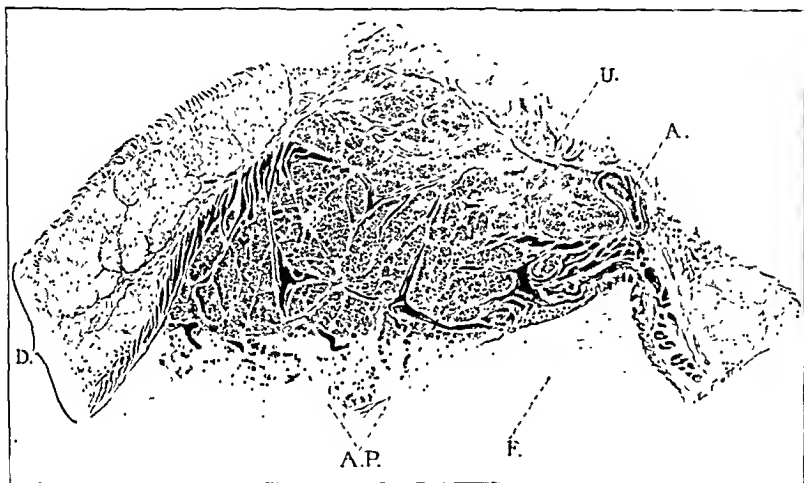


Fig. 6 (case 21).—Camera lucida drawing from microscopic section ( $\times 4$ ) showing aberrant pancreatic tissue in the wall of the duodenum. The duodenal mucosa is absent over the pancreatic tissue, and there is an ulceration in this area. *D.* indicates the duodenal wall; *A.P.*, aberrant pancreatic tissue; *F.*, fat; *U.*, ulceration on the internal surface, and *A.*, an eroded artery from which hemorrhage occurred.

CASE 22.—D. B., a woman aged 66 years, entered the hospital on Sept. 28, 1932, complaining of sour eructations and indigestion of fifteen years' duration. At the onset of the illness there was epigastric pain which occurred twenty minutes after each meal. Roentgen studies of the intestinal tract at that time were said to have given negative results. Recurrence of these symptoms ten years later was followed by a remission. During the past five years the indigestion had been present intermittently. One year before admission the patient had suffered from severe sour eructations after meals. On Sept. 7, 1932, she was admitted because of severe arthritic pains in the left wrist. Roentgen studies of the gastro-intestinal tract showed slight dilatation of the stomach with a residue of from 40 to 50 per cent.

There was a constant filling defect just proximal to the pylorus (fig. 7). The stomach wall, however, was flexible in this area. The changes were interpreted as due to an inflammatory lesion causing partial obstruction of the pylorus.

*Physical Examination.*—This showed a well developed but poorly nourished woman in good general condition. The results of the examination were essentially normal.

*Laboratory Examination.*—Routine studies of the blood and urine gave normal results. Gastric analysis showed free hydrochloric acid equivalent to 50 cc., and total acidity equivalent to 79 cc., of tenth-normal sodium hydroxide. The Wassermann and Hinton reactions of the blood were negative.

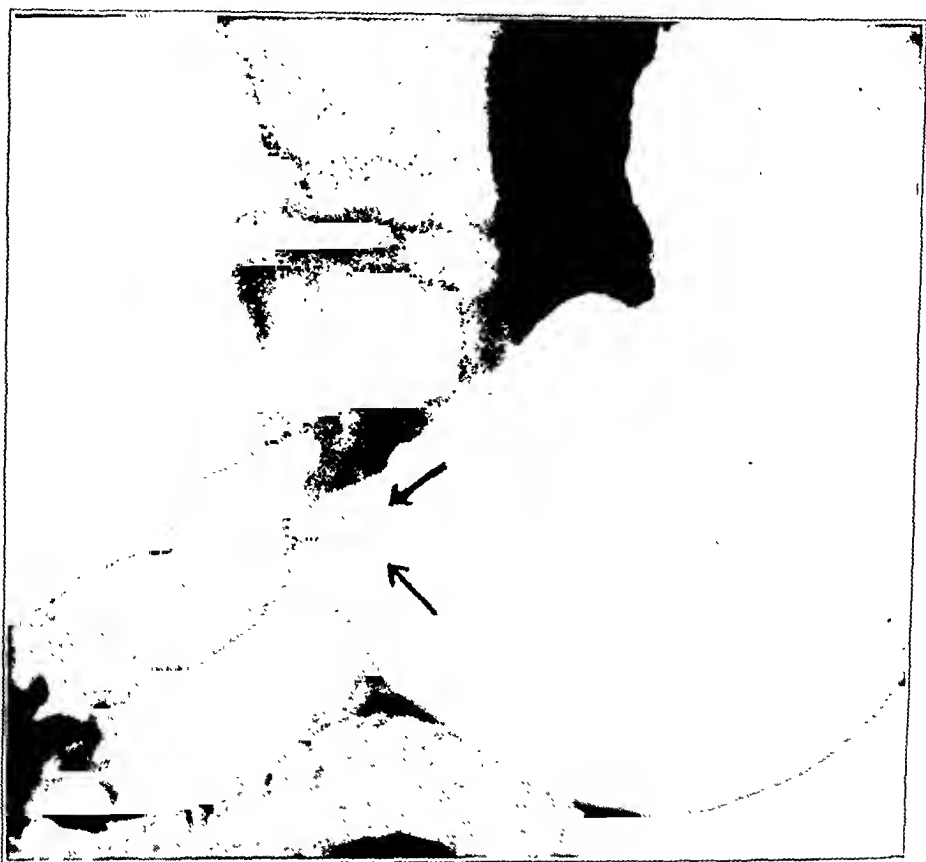


Fig. 7 (case 22).—Roentgenogram showing a filling defect in the gastric antrum produced by a pancreatic nodule projecting in from the posterior wall of the stomach (compare with figure 8).

*Operation.*—On September 29 an abdominal exploration was performed by Dr. Elliott C. Cutler. Palpation of the antral end of the stomach revealed a mass 1 cm. in diameter in the posterior wall of the stomach in the prepyloric area. This projected into the lumen at this site so as to partially obstruct the pylorus. The antral end of the stomach and a part of the duodenum were resected. Reanastomosis was performed by Horsley's method.

The postoperative course was uneventful, and the patient was discharged fifteen days later.

*Gross Pathologic Description.*—No area of ulceration was seen in the gastric or duodenal mucosa. Proximal to the pyloric sphincter there was a small, round,

nodular whitish mass, 1 cm. in diameter. This nodule projected well into the lumen of the gastric antrum (fig. 8). The mucosa covering this nodule was congested. When the mass was cut through it was found to contain a small amount of clear mucus. A small ductlike orifice was found in the mucosa of the duodenum just beyond the pyloric ring. This duct lay at the edge of the nodular mass described and admitted a fine probe for a distance of about 2 mm. in the direction of the nodule. From this orifice a small amount of fluid could be expressed.

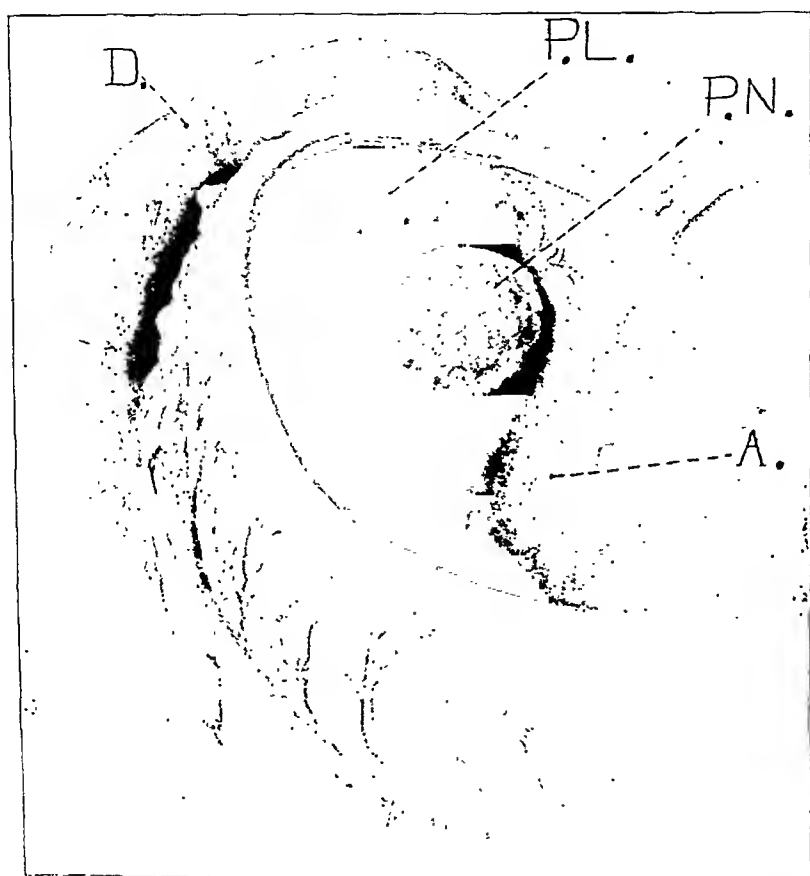


Fig. 8 (case 22).—Drawing illustrating a nodule of pancreatic tissue projecting into the stomach so as to obstruct the pyloric lumen. *A.* indicates the antrum of the stomach; *D.*, the duodenum; *P.L.*, the pyloric lumen, and *P.N.*, the pancreatic nodule.

*Microscopic Examination.*—Serial sections were made of the lesion. The nodule situated in the submucosa consisted of a number of different structures which fused into a single anomalous mass. The nodule was composed mostly of numerous secretory glands and acini which were similar in appearance to Brunner's glands. These drained into ducts which in turn emptied into the intestinal lumen. These ducts were lined by tall columnar epithelium. Intermixed with these glandular



elements were islands of pancreatic acinar tissue, varying from 0.5 to 1.5 mm. in their greatest dimensions. These cells contained secretory granules. The small ducts lined with cuboidal epithelium which drained this acinar tissue emptied in turn into the previously described larger ducts. No islets of the Langerhans type were present. There was no active inflammatory process in the aberrant pancreatic tissue. Overlying the ducts, at a point just proximal to their entry into the bowel, there was a tiny ulcer in the gastric mucosa. This was wholly superficial to the muscularis mucosae and measured about 0.5 mm. in diameter. Its base was formed by a thin layer of fibrin and polymorphonuclear leukocytes which replaced the epithelium.

CASE 23.—J. R., a man aged 69, was admitted to the hospital on Aug. 26, 1931. He complained of constipation of four months' duration. There was a history of considerable loss of weight in the year before admission. Physical examination showed a somewhat emaciated, elderly man with mild abdominal distention. The remainder of the examination disclosed no remarkable features. An enema with barium revealed an irregularity in the first portion of the sigmoid colon, and a diagnosis of carcinoma of the sigmoid colon was made. A cecostomy was established on August 26, and a Mikulicz resection of the sigmoid colon was performed on September 1. Pulmonary complications developed after the operation, and the patient died on September 8.

*Gross Pathologic Description.*—On the anterior surface of the first portion of the duodenum there were seven firm white nodules, varying from 1 to 9 mm. in diameter. At the time of autopsy these were thought to represent implantations from the colonic carcinoma. There was no ulceration of the mucosa on the internal aspect of the duodenum.

*Microscopic Examination.*—The largest nodule was 9 mm. in diameter and 4 mm. in maximum thickness. It partially replaced the submucosa and the muscularis. In a few places it protruded up through the muscularis mucosae, but it was entirely covered by duodenal epithelium. In a few places it extended through the muscularis. It was entirely covered on its external surface by serosa of the duodenum. This nodule consisted largely of ductal elements of varying size. Some of these were lined with cuboidal epithelium; others were lined with a columnar type of epithelium. In many areas there were numerous small ductules. There were a few small islands of cells of the pancreatic acini type, but these elements were much less prominent than the duct formations. There were no cells of the Langerhans islet type. This aberrant pancreatic tissue had a moderate stroma, scattered through which there were occasional lymphocytes. There was no evidence of an active inflammatory process. Bundles of duodenal musculature coursed through this aberrant tissue. The remaining nodules were all from 1 to 3 mm. in diameter. They were situated external to the duodenal muscularis but were all covered by the serosa. These smaller structures all showed essentially the same histologic structure as did the larger nodule.

CASE 24.—E. L., a woman aged 82, entered the hospital on May 21, 1934, with the complaint of cough, fever and pain in the chest. A typical bronchial pneumonia developed, and the patient died on the fourth day of hospitalization.

The past history revealed that the patient had had some sour eructations four years previously. She was admitted to the hospital at that time, and roentgen studies showed no evidence of abnormality of the stomach or duodenal cap. Examination of the stool at that time showed 4+ reactions to benzidine and guaiac tests. These reactions were not obtained on subsequent examination.

*Pathologic Description.*—On the anterior surface of the second portion of the duodenum there was a projecting, finger-like diverticulum, 3 cm. in length and 1.5 cm. in diameter. Over the distal three fourths of the diverticular surface there was a caplike thickening beneath the serosa which varied from 1 to 4 mm. in thickness. This was finely lobulated and pinkish gray and grossly suggested a thin sheet of aberrant pancreatic tissue distributed over the surface of the diverticulum. The inner surface of the diverticulum showed no ulceration or scarring of the mucosa.

*Microscopic Examination.*—The aberrant pancreatic tissue was found in the submucosa, scattered through the muscularis which it divided into separated bundles, and in the adjacent serosal fat (fig. 9). The major part of this substance duplicated closely the architecture of normal pancreas. There was a normal arrangement of acinar cells into primary and secondary lobules. The islets of



Fig. 9 (case 24).—Photomicrograph ( $\times 15$ ) of aberrant pancreatic tissue occurring in the wall of a duodenal diverticulum.

Langerhans were numerous and large. The stroma of most of the tissue had about the same prominence as that observed in normal pancreas, but in a few areas, particularly toward the inner parts of this tissue, there were broad zones of dense stroma in which there were many dilated ducts. Some of these ducts apparently emptied into the lumen of the diverticulum. The mucosa was duodenal in type, but the Brunner glands were not numerous. There was no ulceration or scarring of the mucosa, but lymphoid elements in the tunica propria were quite prominent.

#### COMMENT

Twenty-four cases in which aberrant pancreatic tissue was discovered at examination of autopsy material or of surgical pathologic specimens are reported in this series. Twelve of the patients were males, and

twelve were females. The youngest patient was 8 days old and the oldest was 82. The majority of these anomalies were found at autopsy; in only five cases was the aberrant tissue identified during the course of an abdominal operation. In two of the cases the aberrant pancreatic tissue was located in the wall of the stomach, and in each of these a partial resection of the stomach was performed because it was thought that the nodular structure was carcinomatous. The pyloric ring was the site of the pancreatic tissue in one patient. The anomaly was found in the duodenum in ten cases; in one of these the pancreatic substance was located in the wall of a duodenal diverticulum. Four of the nodules occurred in the jejunum, and one in the ileal wall. In the remaining six cases the pancreatic tissue occurred in a Meckel diverticulum.

The masses of aberrant pancreatic tissue varied in size, as is shown by the summary in the table. The nodules were often flattened and were from 5 to 8 mm. in diameter. The largest single mass was 3 cm. long, 2 cm. wide and 0.5 cm. thick. Another specimen was 1.5 cm. in diameter and 7 mm. in thickness. A third nodule was 1 cm. in diameter. In another case an entire duodenal diverticulum, 3 cm. in length and 1.5 cm. in diameter, was capped by aberrant pancreatic tissue from 2 to 5 mm. in thickness.

The pancreatic tissue was present in various portions of the intestinal wall. Figure 1 shows such a nodule lying in the submucosa covered on the inner surface by mucosa and externally by muscularis. Figures 2, 3 and 9 show islands of pancreatic tissue occurring in intestinal diverticula. Histologically the aberrant substance, as a rule, closely resembled normal pancreatic tissue, showing normal-appearing acinar lobules, stroma, ducts and islets of Langerhans. In fifteen of the specimens there were no islets in the sections studied; in the remaining nine cases, typical islets were identified (fig. 4). In most of the cases in which islets were not seen the microscopic structures were similar to those of normal pancreatic tissue with this one exception. A few specimens showed a great overgrowth of ductal elements as compared with the acinar structures (fig. 5). The presence of zymogen granules in acinar cells indicated that this aberrant tissue was usually functioning.

The aberrant pancreatic tissue was the site of a pathologic lesion in four of the twenty-four cases. In one of these (case 22) operation was performed because of a fifteen year history of sour eructations and indigestion with epigastric pain after meals. Roentgenograms had disclosed a partial obstruction of the pylorus (fig. 7). At the time of operation the cause of obstruction proved to be aberrant pancreatic tissue which projected into the gastric lumen and obstructed the outlet of the stomach (fig. 8). Resection of this mass has effected complete relief of symptoms. In the second case (case 21) there had been repeated attacks of vomiting for several months with an associated loss of weight

and the onset of general weakness. Examination of the stools by means of benzidine and guaiac tests had shown the presence of blood. Pneumonia developed, and the case terminated fatally. At autopsy a bleeding ulcer was found in the first portion of the duodenum. On microscopic examination, this proved to be ulcerated aberrant pancreatic tissue, in which there was a large eroded artery that had ruptured because of the ulcerative process in the pancreatic substance (fig. 6). The duodenal ulceration was obviously the important lesion in this case and was the cause of the chronic illness. In the third case (case 16) there was a gastric ulcer in the inflammatory mass of which were found many small "nubbins" of pancreatic tissue. Since the removal of the lesion there have been no gastric symptoms. In the fourth case (case 7) the specimen proved to be a bleeding ulcer of the duodenum; it was found at autopsy; its existence had not been suspected during the patient's life.

From the study of this series of cases there is little to support any one theory as to the genesis of aberrant pancreatic tissue, but the material lends strong support to the belief that such a nodule of pancreatic substance is antenatal in origin. It seems most probable that the occurrence of aberrant pancreatic tissue is a congenital abnormality which arises either as an anomalous anlage or as an inclusion of primitive pancreatic tissue in a portion of the foregut or its derivatives. Although King and MacCallum expressed the belief that pancreatic acinar tissue may arise from the gastric epithelium under the influence of a chronic inflammatory reaction, we are strongly opposed to this theory as the proper etiologic explanation in the majority of cases. In support of their contention, King and MacCallum called attention to the fact that all their patients were elderly persons; they assumed from this fact that pancreatic tissue did not appear until in adult life, when ulceration or inflammatory change in the gastric epithelium had occurred. Our observations contradict this view, for thirteen of our patients were under 12 years of age and eight of these were in the first year of life. Furthermore, in the majority of our cases there was no evidence of an active inflammatory process or of old scarring in the pancreatic tissue to indicate that inflammatory lesions had instigated a metaplasia and the formation of pancreatic tissue. The view that aberrant pancreatic tissue is an atavistic phenomenon is also not acceptable, for there is no record of pancreatic tissue having this wide dissemination in a human embryo at any stage in its development. The finding of such an embryologic stage would be necessary if the phylogenetic theory were the proper explanation. We are therefore of the opinion that these aberrant masses of pancreatic tissue represent congenital anomalies, that they are the result of aberrations from the normal development and do not represent a stage normally present in fetal growth.

## SUMMARY

Approximately two hundred cases in which aberrant pancreatic tissue was found have been recorded in the literature. In the majority of these the tissue occurred in the gastro-intestinal tract. This report adds twenty-four other cases in which aberrant pancreatic tissue was found in various locations in the wall of the alimentary canal. The distribution was as follows: In three instances the tissue was found in the stomach or pylorus; in ten, in the duodenum (in one in a duodenal diverticulum); in four, in the jejunum; in one, in the ileum, and in six in a Meckel diverticulum. These structures contained ductal and acinar elements the histologic structure of which closely resembled that of normal pancreatic tissue. In fifteen specimens there were no islets of Langerhans in the sections studied, but in the other nine cases there were typical islets. The age of the patients in whom the anomalous tissue was found varied from 8 days to 82 years. The cases occurred in equal numbers in males and in females. The presence of this aberrant pancreatic tissue in the gastro-intestinal tract probably represents a congenital anomaly in most, if not in all, instances.

Four of these twenty-four cases had important pathologic significance. In one of these the nodule caused pyloric obstruction, and in the other three it was the site of ulceration in the stomach or duodenum.

Such a nodule in the wall of the gastro-intestinal tract has been mistaken for carcinoma. The gross appearance of the tissue should indicate that it is pancreatic in type and should obviate the danger of unnecessary removal when it is not the cause of intestinal obstruction or the site of an important pathologic lesion.

# ULCERATIVE COLITIS

STUDY OF BACTERIA IN THE ISOLATED COLONS OF THREE  
PATIENTS BY CULTURES AND BY INOCULATION OF  
MONKEYS

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Ileostomies are occasionally made in patients with severe ulcerative colitis for the purpose of putting the colon at rest. In some of these patients, the colon does not heal following operation and rectal discharges of blood-streaked purulent material may persist for years.<sup>1</sup> A study of the kinds of bacteria inhabiting the isolated diseased colon, in the absence of organisms maintained by a fecal current, should extend knowledge of the bacteriology of ulcerative colitis.

In this investigation a bacteriologic study was made of the contents of the isolated colon in three patients with ulcerative colitis, in each of whom an ileostomy had been performed. These patients were as follows: (1) Mrs. N., aged 21 years, in whom an ileostomy was performed on April 21, 1933; (2) Mrs. P., aged 29 years, in whom an ileostomy was performed on Oct. 18, 1933, and (3) Mrs. S., aged 47 years, in whom an ileostomy was performed on Sept. 22, 1931. In an attempt to evaluate the significance of certain organisms isolated from these patients, some experiments were carried out with monkeys (*Macacus rhesus*), rabbits and guinea-pigs.

The specimens used in this study were usually obtained by passing a sterilized soft rubber urethral French catheter into the rectum and aspirating material through this catheter into a sterile syringe. In many cases it was necessary to introduce a few cubic centimeters of sterile saline solution into the bowel in order to obtain an adequate sample. Some cultures were taken from the lesions on a swab at the time a proctoscopic examination was made. The specimens were always mucopurulent and somewhat blood-tinged.

The material was examined for amebas, and smears were made on slides and stained with Wright's stain in order to study the types of cells present. Gentian violet stains were also made to reveal any spirochetes or fusiform bacilli. Finally a Gram stain was made to differentiate the types of bacteria. No amebas, intes-

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From the Department of Hygiene and Bacteriology, the Department of Medicine and the Department of Surgery, the University of Chicago.

<sup>1</sup> Barga, J. Arnold; Brown, Philip W., and Rankin, Fred W.: Surg., Gynec. & Obst. 60:196, 1932.

tinal spirochetes or fusiform bacilli were ever found. No unusual cell types were present in the bloody mucopurulent specimens.

A few specimens, taken by swabbing the lesions at proctoscopic examination, were put into dextrose brain broth, and after six hours' incubation at 37 C. in this medium the growths were streaked on blood agar plates. Gram-positive diplococci were sometimes demonstrated but were frequently absent.

Eosin methylene blue plates were always streaked with the original specimen for isolation of dysentery organisms, but none were ever found.

Decimal dilutions were made of the specimens in saline dilution blanks, and 1 cc. portions of the various dilutions were put into dextrose beef heart medium (1 per cent dextrose added to Robertson's<sup>2</sup> beef heart meat medium) and into lactose broth fermentation tubes. The former was an excellent medium for the growth of streptococci, *Bacteroides* (anaerobic gram-negative and gram-positive nonsporulating rods), *Bacillus acidophilus* and many other types of organisms. This medium was so prepared that the supernatant fluid above the ground meat was clear; growth was indicated by turbidity.

Blood agar plates (10 per cent sheep blood in veal infusion agar base) were streaked directly with the specimens. Some were incubated aerobically and others anaerobically. The anaerobic blood agar plates were placed in large pyrex vacuum desiccators, and the pressure was reduced to the vapor tension of water. One atmosphere of carbon dioxide was then admitted, and the jar was exhausted to the vapor tension of water, placed in the incubator and incubated at 37 C. for four days. A solution of pyrogallie acid and sodium carbonate was kept in the bottom of the anaerobic jars to remove traces of the oxygen which was slowly given up from the blood in the medium.

With patient 1, specimens were collected from the colon at intervals of two weeks for a period of two months following the operation. After that time monthly examinations were made. With the second patient, fifteen specimens were collected at weekly intervals after the operation. With the third patient, only two specimens were taken, three months apart and two and one-half years following the operation. The organisms isolated from the first two patients immediately following the operation were essentially the same as those commonly encountered in fecal examinations. There was, however, a marked change in the type of organisms predominating in the bowel. During this transition from one type of flora to another, an organism of the genus *bacteroides* was recovered from the highest dilutions of the specimens put into beef heart dextrose medium. This organism was an anaerobic, small, gram-negative, nonsporulating rod which formed acid in dextrose, sucrose, lactose and glycogen, but failed to ferment glycerol, mannitol, sorbitol, arabinose, salicin and rhamnose. It did not liquefy gelatin or form indol in tryptophan broth. Strains with similar reactions were recovered from the isolated normal colons of two monkeys.

The flora of the isolated colons of patients 1 and 2 ultimately resembled that found in the colon of the third patient, in whom ileostomy had been performed two and one half years before, the colon having been undisturbed during that time. This type of flora was demonstrated

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2. Robertson, M.: *J. Path. & Bact.* 20:327, 1915-1916.

fifteen months after ileostomy in patient 1 and ten weeks after ileostomy in patient 2. The length of time required for the flora of patient 1 to become similar to that of the others was due to the fact that organisms of the *Proteus* type appeared and persisted in large numbers in the colon following the operation, overgrowing other types on artificial mediums. After fifteen months, however, these organisms had disappeared, and the flora of this patient resembled that of the other two.

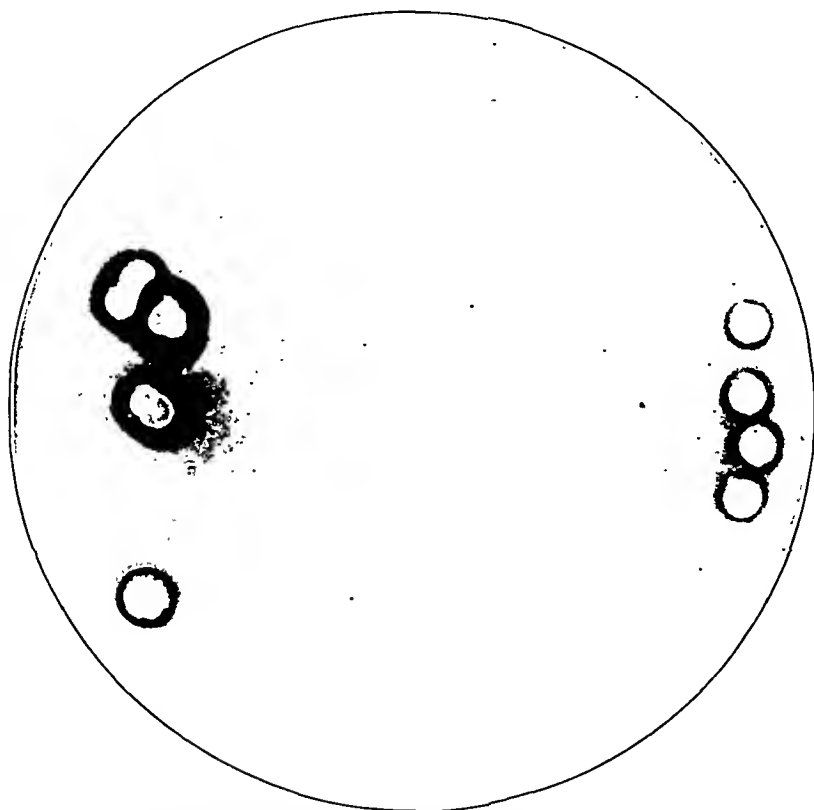


Fig. 1.—Blood agar plate streaked with specimen from Mrs. P., Dec. 22, 1933, and incubated aerobically for four days at 37 C.

At this stage few colon bacilli were present, and the flora was predominantly anaerobic. Few colonies appeared on aerobic blood agar plates, but thousands of colonies were present on similar plates streaked with the same amount of material and incubated anaerobically. Two types of bacteria growing on anaerobic blood agar plates were common to the three patients and greatly outnumbered all other organisms. They were (1) the predominant organism, to be described later, and (2) a strictly anaerobic nonhemolytic organism which formed a pinpoint-size colony and which proved to be a gram-negative streptococcus. The



latter was not pathogenic for guinea-pigs when injected subcutaneously (figs. 1 and 2).

The colonies of the predominant organism were round, grayish and raised, measuring, when well isolated, from 0.5 to 1 mm. in diameter (fig. 3). When the plates were removed from the desiccators they had a putrid odor resembling somewhat that of butyric acid. There was no zone of hemolysis about these colonies when first removed from the

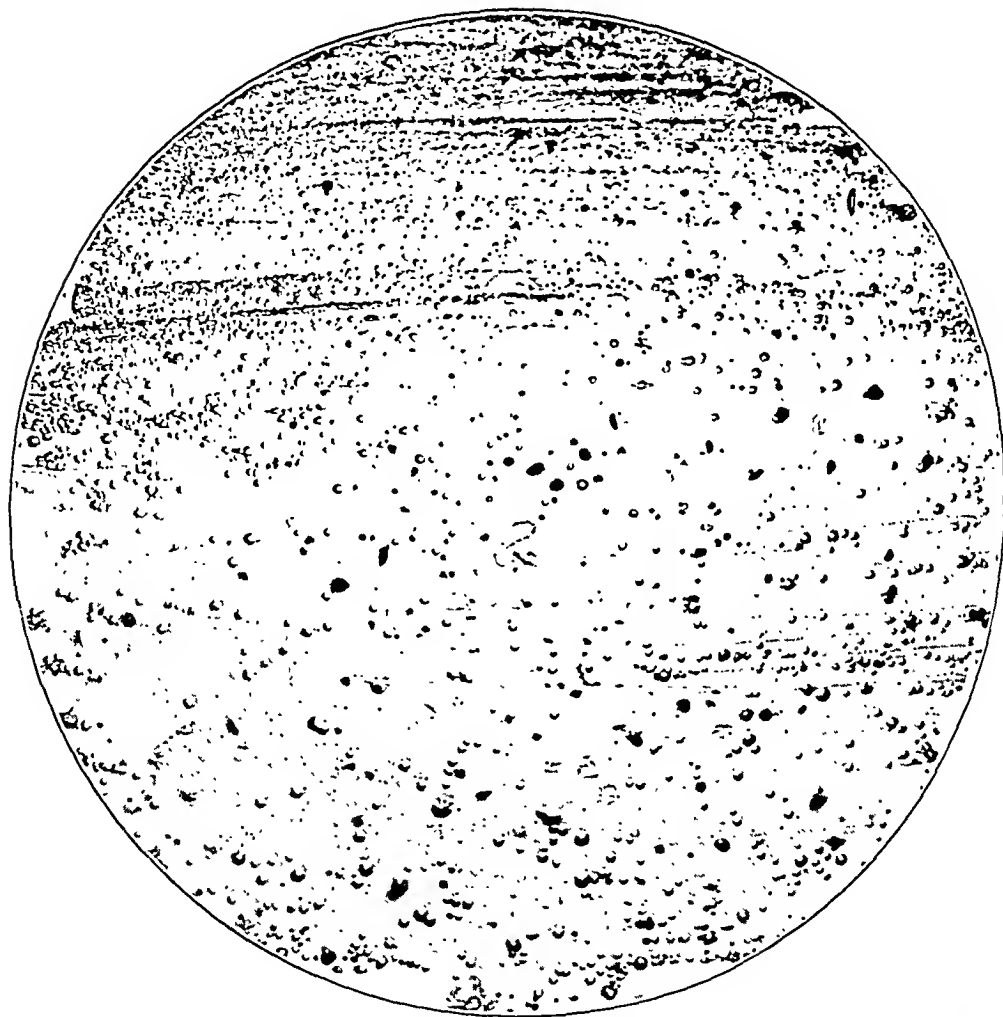


Fig. 2.—Blood agar plate streaked with specimen from Mrs. P., Dec. 22, 1933, and incubated anaerobically for four days at 37 C.

anaerobic environment, but as oxygen was taken up by the hemoglobin in the blood a greenish zone of hemolysis appeared around them.

When picked from the plates the colonies had a tendency to stick together. In smears they appeared as gram-negative rods and filaments (shown in figs. 4 and 5). Many of the cells stained faintly and appeared as "ghost" forms. Often a long filament would stain irregularly, and bulges would appear in portions of it. The organisms occasionally grew anaerobically, but never aerobically, when transferred to blood agar

slants. After a strain was started from a single colony it could be readily maintained by transferring a large amount of the growth to blood agar slants and incubating anaerobically. The organisms did not grow in veal infusion mediums or in dextrose beef heart or dextrose brain broth. Good growth occurred in dextrose cystine agar, recommended by Shaw.<sup>3</sup> If another carbohydrate was substituted for dextrose in the cystine agar, growth often did not appear. The organism

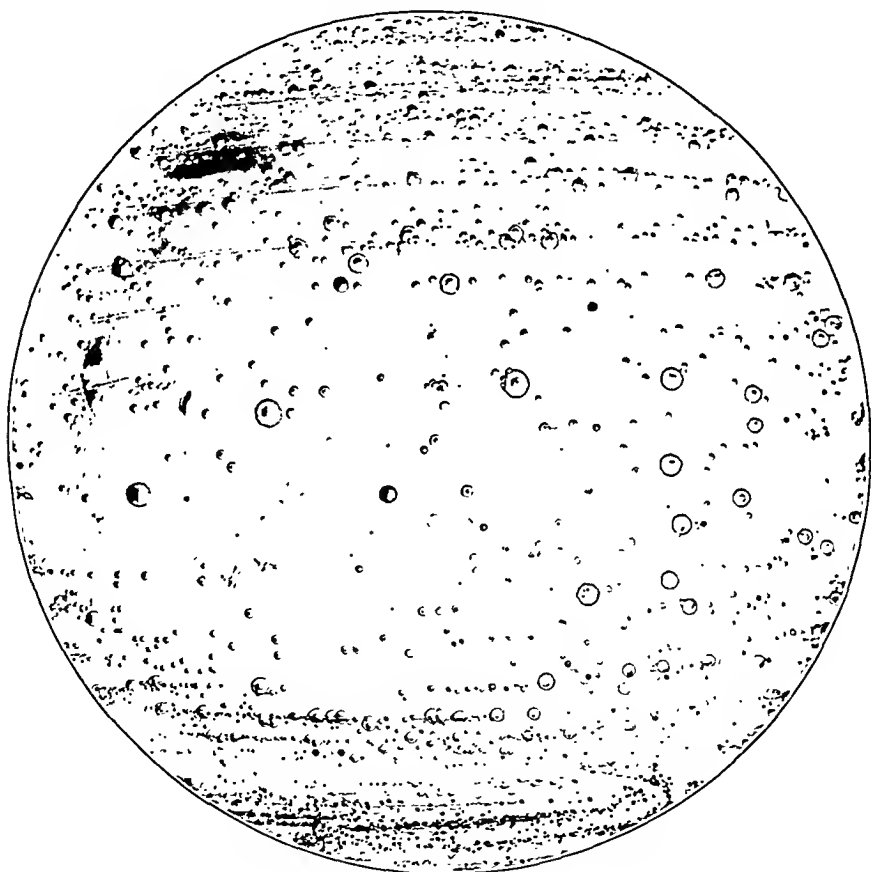


Fig. 3.—Colonies on blood agar plate streaked with specimen from Mrs. S. (taken May 12, 1934) and incubated four days in an anaerobic jar at 37 C. The largest colonies are those of *Proteus*. The predominant colony is surrounded by a zone of green hemolysis, which does not appear in the photograph. A few tiny pinpoint-size colonies are present, which in smears showed gram-negative streptococci. Some areas may be seen where colonies were scraped off for staining.

also grew in sheep serum (20 per cent) dextrose veal infusion broth under anaerobic conditions. When dextrose was replaced by another carbohydrate in the serum broth, growth frequently did not occur. The

3. Shaw, Frederick W.: Zentralbl. f. Bakt. (Abt. 1) **129**:132, 1933.



Fig. 4.—Strain 11 on anaerobic blood agar plate incubated four days at 37 C. Colony stained by Gram's method;  $\times 2,000$ .

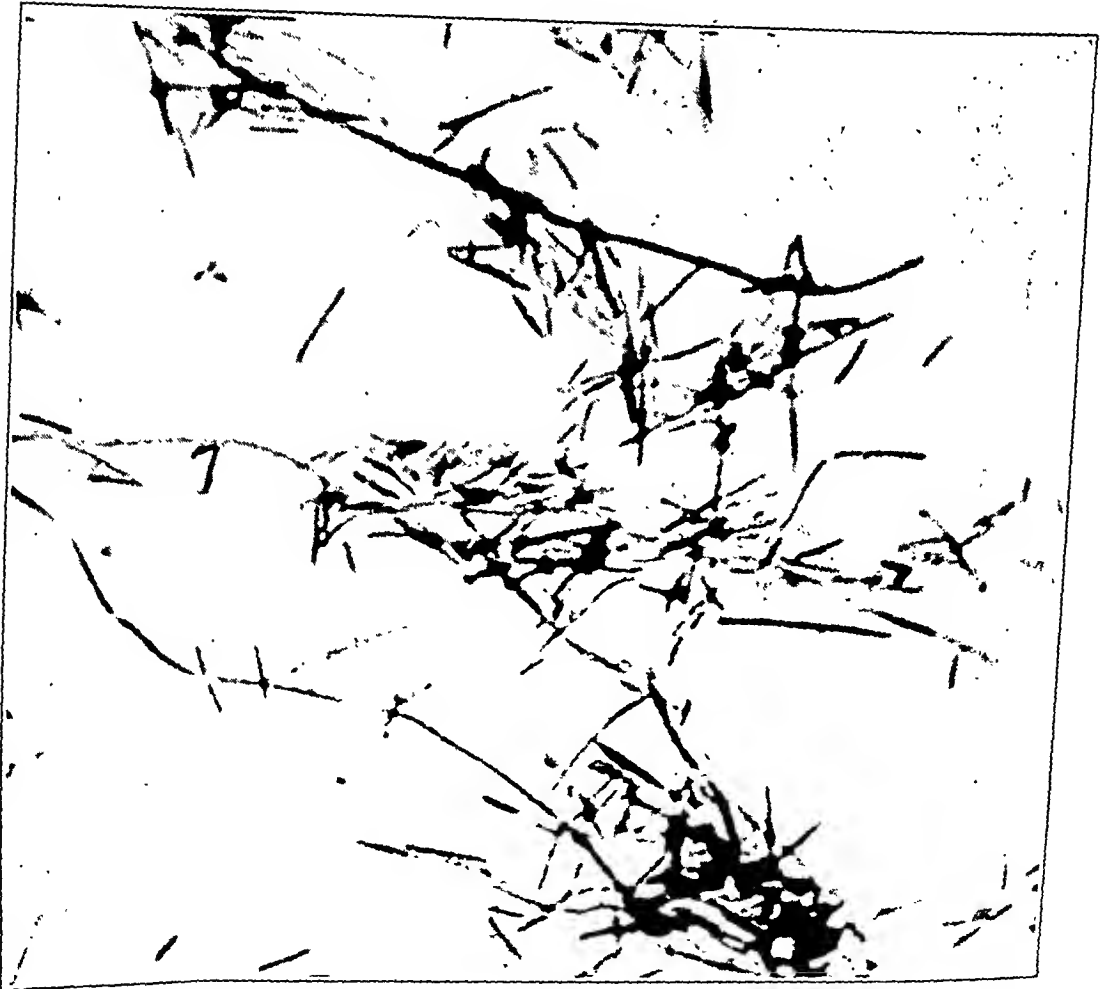


Fig. 5.—Strain 40 on anaerobic blood agar plate incubated four days at 37 C. Colony stained by Gram's method;  $\times 2,725$ .

biochemical reactions were tested after fourteen days' incubation of the tubes in an anaerobic jar. Acid was produced in dextrose medium, but lactose, sucrose, salicin, inulin, mannite and glycerin were not broken down. Milk was unchanged. The strain isolated from patient 1 liquefied gelatin in one of two tests with gelatin serum medium, but failed to do so in two tests with gelatin cystine medium. The other strains, with the exception of strain 39, did not liquefy gelatin.

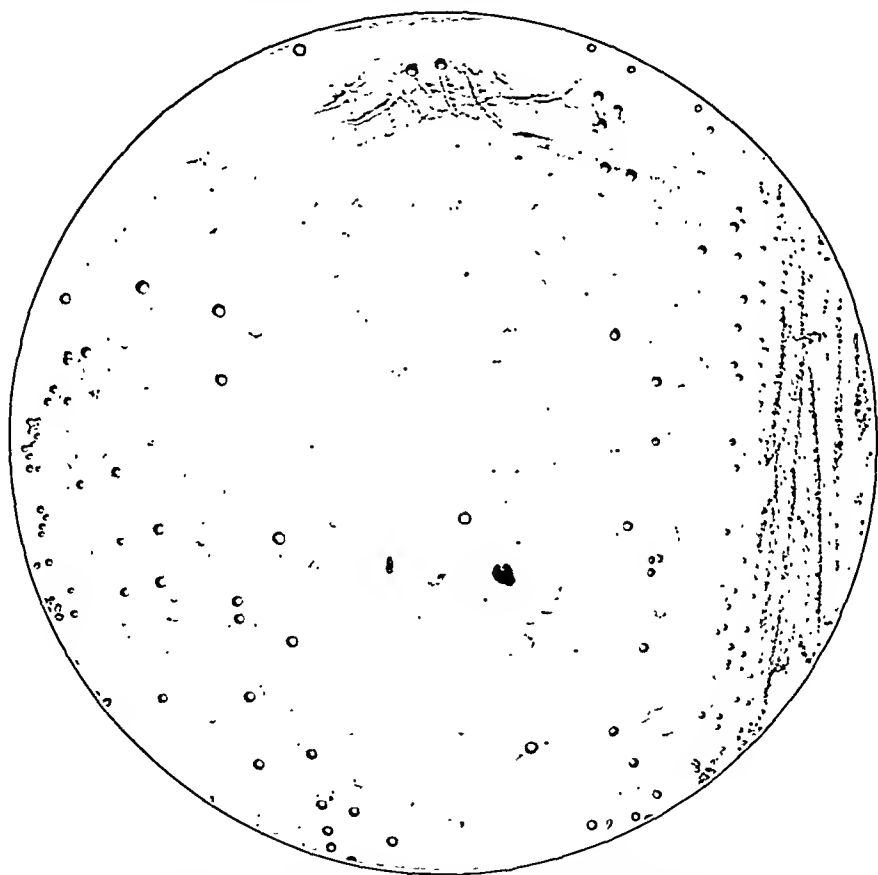


Fig. 6.—Anaerobic blood agar plate streaked with pus obtained from an abscess in a rabbit eight days after subcutaneous injection of strain 11. The plate had been incubated four days at 37 C.

Four strains were studied in animals. These were: strain 40 from patient 1, strain 11 from patient 2, strain 38 from patient 3 and strain 39 from monkey 6, which died of bacillary dysentery (Flexner type).

Rabbits inoculated subcutaneously with the growth from anaerobic blood agar plates heavily inoculated with these strains acquired abscesses at the sites of injection. Pure cultures of the organisms were obtained when anaerobic blood agar plates were streaked with the thick creamy

pus found in the abscesses (fig. 6). Gram-negative rods were found in the stained pus (fig. 7). No filaments were observed. The abscesses either drained spontaneously or were absorbed. No lesions other than the local abscesses followed the subcutaneous injection of these cultures into rabbits. Guinea-pigs inoculated subcutaneously in the groin with strain 11 and with an anaerobic gram-negative streptococcus isolated from the colon specimen of patient 2 on Jan. 19, 1934 did not

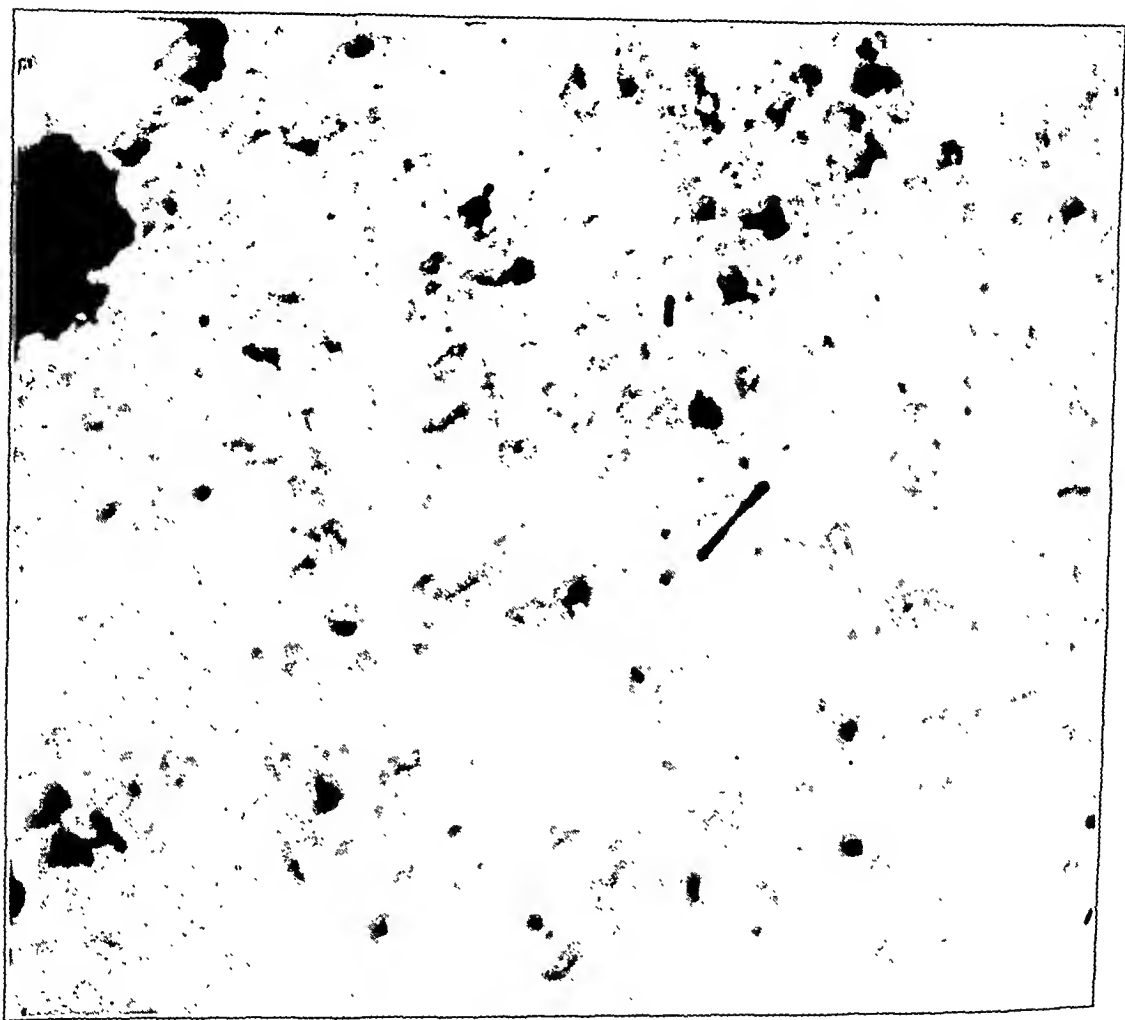


Fig. 7.—Gram stain of a smear of pus aspirated from an abscess in a rabbit fifteen days after subcutaneous injection of strain 38;  $\times 2,725$ .

present abscesses or appear ill. Mixtures of these two organisms also failed to produce symptoms when similarly administered.

These filamentous gram-negative anaerobic organisms were not found in the stools of four healthy monkeys, although eight different examinations were made. However, from one monkey (6), which died after contracting a spontaneous bacillary dysentery (Flexner type), a similar organism was isolated on an anaerobic blood agar plate streaked

with mucopurulent material taken from the descending colon. At necropsy on this animal no gross pathologic change was observed except in the colon. The serosa was injected throughout and that in the descending colon showed small petechial hemorrhages. When the large bowel was opened, the mucosa appeared grossly edematous, was covered with mucopurulent material and contained numerous pinhead-sized superficial ulcerations. This strain resembled very closely the others obtained from the diseased colons of patients 1, 2 and 3, and was designated as strain 39. A Flexner dysentery organism was cultured from the same specimen.

A monkey (C P) with an isolated cecum and ascending colon was operated on, May 7, 1934, at which time the isolated bowel was resected. After the operation there was considerable drainage from the wound. About ten days following the operation the animal presented a profuse watery diarrhea which persisted for two or three weeks. On May 22, a proctoscopic examination was made, at which time the mucosa of the lower part of the colon was found to be very hyperemic. Through the proctoscope a swab was rubbed over the mucosal surface, and blood agar and eosin methylene blue agar plates were streaked. Some of the blood agar plates were incubated anaerobically and others aerobically. Numerous colonies resembling those of *Bacterium coli* grew on the eosin methylene blue plates and aerobic blood agar plates. On the anaerobic blood agar plates numerous green hemolytic colonies appeared which were indistinguishable morphologically from culture 39 or strains 11, 38 and 40. One colony was picked and put on two blood agar slants. One was incubated aerobically and the other anaerobically. Neither culture grew, which conforms with previous experience. Complement-fixation tests were made on the serum of this monkey.

Rectal mucosa was removed from each of two monkeys. One of these animals (1) had been fed culture 11 on March 20, 1934, and a similar organism was isolated from the bowel two days later. On four subsequent weekly examinations no typical green hemolytic colonies were found. A spontaneous prolapse of the rectum occurred in this monkey following a proctoscopic examination on April 23. When prolapse of the rectum was produced, an area of mucosa about a centimeter in diameter was removed with forceps and a scalpel. Three days later another proctoscopic examination was made, and prolapse again produced. A thick grayish necrotic membrane covered the previously denuded area. Part of this membrane was dissected off and cultured immediately. Numerous well isolated green hemolytic colonies developed on anaerobic blood agar plates. There were two types of these colonies: One type resembled strain 39 in every detail. The other type of colony was flat, smooth and somewhat larger than that resembling strain 39 and

was made up of uniform long slender gram-negative rods which were pointed at the ends. Both types of colony were anaerobic. Portions of rectal mucosa were removed from this animal three different times during a period of three weeks. Each time the necrotic membrane over the lesion was cultured, and each time the same types of colonies grew out on anaerobic blood agar plates. Eighteen days after the first removal of the mucosa, prolapse of the rectum was produced, and the growth from six anaerobic blood plates of strain 38 was taken up in sterile saline solution and injected submucosally into a portion of the rectum which had not previously been denuded of mucosa. The bowel was made to prolapse and was examined three days later, and no ulcerations or lesions were seen about the site of injection. Complement-fixation tests were made with the serum of this monkey.

The second monkey (2) was anesthetized with pentobarbital sodium, and a low midline incision was made above the symphysis pubis. The rectum was invaginated over a gloved finger and a portion forced out through the anal sphincter. A second operator then denuded the mucosa of the portion of bowel over the finger. When the bowel was replaced no perforation was seen. Cultures were taken through a proctoscope two days later. The anaerobic blood agar plates were overgrown with a spreading *Proteus*-like organism. However, one green colony was seen in mixture with the *Proteus*-like spreader. This colony, when picked and stained, appeared to be made up of long gram-negative rods and filaments and corresponded to strain 39 and the other similar strains, 11, 38 and 40. Complement-fixation tests were also made with the serum of this monkey.

Two monkeys were fed culture 11 by stomach tube; one received a saline suspension of the growth from three anaerobic blood agar plates, and the other the growth from four similar plates. No symptoms developed in these animals. From a colon specimen taken forty-eight hours after feeding the organism to one of the monkeys (1) an isolated green colony developed on an anaerobic blood agar plate. This colony, when stained, resembled the type of organism which had been fed this animal. A *Proteus*-like organism overgrew the anaerobic blood plate culture from a specimen taken forty-eight hours after feeding the other monkey (3).

#### COMPLEMENT-FIXATION TESTS

Strains 11, 38, 39 and 40, when grown anaerobically on blood agar plates, were found to be unsuitable as antigens for agglutination tests, since the growth removed from these plates was clumped. The antigens in the complement-fixation tests were prepared by heavily streaking about fifteen blood agar plates with each strain. The plate cultures were

put in anaerobic jars and incubated for four days at 37 C. The plates were then removed from the desiccators, and the growth was rinsed off with sterile saline solution. It was necessary to use a large wire loop to loosen the growth, as it adhered to the blood agar medium. This growth, when removed, was taken up in about 5 to 6 cc. of saline solution. The suspensions were placed in 15 cc. pyrex centrifuge tubes and alternately frozen and thawed. Freezing was accomplished by putting small blocks of carbon dioxide snow into alcohol and dipping the tubes containing the suspensions into this mixture. After thorough freezing the tubes were held under a hot water faucet, and water at a temperature of 45-50 C. was run over them until the frozen contents were melted. Each antigen was frozen and thawed twenty times. After the final freezing the tubes were centrifugated at high speed for one hour. The supernatant fluid was diluted to 15 cc. with sterile saline solution, placed in sterile vaccine bottles and kept frozen in an electric refrigerator until used. Smears were made of the sediment, but it was difficult, in view of the staining reactions of these organisms, to tell how much autolysis was accomplished by freezing and thawing. The sediment was therefore discarded.

The antigens were not hemolytic or anticomplementary in a 1:4 dilution, so that this dilution was used in the tests. The Kolmer method was followed, using icebox fixation. Antigen 40 did not prove to be antigenic with any of the serums with which it was tested, and for that reason the results from the use of it are not included in the tables (tables 1 and 2).

The complement-fixation test indicated the presence of antibodies in the serum of patients with ulcerative colitis. The antibody titers were not high in any case, but they were greater in the more severe cases (patients 2 and 3 and Mr. L.). No complement-fixing antibodies were found in the serum of patient 1. Following the ileostomy this patient had greatly improved clinically, which might account for the negative tests with her serum.

The results of the complement-fixation tests on monkeys were variable. Following removal of rectal mucosa the antibody titer of the serum of monkey 1 increased, whereas the titer of the serum of monkey 2 was somewhat lower after an operation in which some rectal mucosa was removed. The initial high titer of antibody in the case of monkey 2 may represent a previous ulceration of the bowel in which the antigen in question was present. Epidemics of bacillary dysentery are common in monkeys in captivity, and unless one knows the history of a given monkey one cannot be sure that there was not a previous ulceration of the bowel.



TABLE 1.—*Complement-Fixation Tests on Serum of Patients with Ulcerative Colitis*

Source of Serum with Date Serum Was Taken	Antigen	Result of Test with Serum*	
		0.1 Ce.	0.05 Ce.
Patient 1 (Mrs. N.), 12/16/33 and 6/2/34.....	11	—†	—
	38	—	—
	39	—	—
Patient 2 (Mrs. P.), 1/19/34.....	11	++	—
	38	+++	—
	39	—	—
Patient 3 (Mrs. S.), 5/12/34.....	11	+++	—
	38	++++	±
	39	+	—
Patient with ulcerative colitis (Mr. L.), 5/12/34.....	11	+++	—
	38	++++	—
	39	±	—
Patient with ulcerative colitis (Mr. T.), 5/12/34.....	11	+	—
	38	++	—
	39	±	—
Young woman without history of bowel lesion (Mrs. G.)	11	+	—
	38	+	—
	39	—	—
Four healthy young adults.....	11	—	—
	38	—	—
	39	—	—

\* There was no fixation of complement with 0.025 cc. of serum. Serum controls were not anticomplementary in 0.1 cc.

† A minus sign indicates complete hemolysis; four pluses, no hemolysis.

TABLE 2.—*Complement-Fixation Tests on Serum of Monkeys*

Monkey Serum	Date of Collecting	Treatment of Animal	Antigen	Result of Test with Serum		
				0.1 Ce.	0.05 Ce.	0.025 Ce.
1	5/ 1/34	Serum taken 9 days after removal of rectal mucosa. Rectal mucosa removed 4/23/34	11	++	±	—
			38	++	±	—
			39	++	±	—
1	5/21/34	More rectal mucosa removed 5/1/34 and 5/9/34. Growth from 6 anaerobic blood agar plate cultures, strain 38, injected submucosally into area of rectum not previously denuded	11	++++	++++	++++
			38	++++	++++	++++
			39	++++	++++	++
1	8/ 4/34	No further treatment.....	11	++++	++++	+
			38	++++	++++	++
			39	++++	++	—
CP	5/28/34	Had severe diarrhea beginning 10 to 11 days before sample of blood was taken	11	++++	++	+
			38	++++	++++	+
			39	++++	+	—
CP*	8/ 3/34	Animal was well and healthy.....	11	++++	++	+
			38	++++	++++	+
			39	++++	++	+
2*	7/17/34	Laparotomy was done 7/17/34 and mucosa removed from rectum	11	++++	++	+
			38	++++	++++	—
			39	++++	+	—
2	8/ 1/34	Animal was well; bowel had healed.....	11	+	—	—
			38	++++	++++	—
			39	+	—	—

\* Serum slightly anticomplementary; ++ with 0.1 cc. serum; — with 0.05 cc. serum.

AGGLUTINATION TESTS<sup>4</sup>

The first attempts to use cultures grown on anaerobic blood agar plates as antigens in agglutination tests were unsuccessful, as growth removed from these plates tended to stick together in large clumps. Successful antigens were prepared for strain 40 by growing the organism in cystine dextrose beef infusion broth<sup>3</sup> put up in 50 cc. quantities in



Fig. 8.—Strain 40; anaerobic cystine dextrose broth culture incubated four days at 37 C. Giemsa stain;  $\times$  2,100.

flasks and incubated under anaerobic conditions in a desiccator, as previously described. After four days' incubation the growth was centrif-

4. During the progress of the work, two of the strains, 11 and 38, failed to grow following an accident which happened to the desiccator in which the cultures were being incubated. The lid of the desiccator was cracked, thus admitting air and destroying the anaerobic conditions. Strains 39 and 40, however, grew on subculture and were used in later studies.

ugated and the sediment resuspended in sterile 0.85 per cent solution of sodium chloride. The organisms grown in this broth were fusiform, with very pointed ends, and the cells were irregular in staining (fig. 8).

They were gram-negative, and some seemed to contain granules. They were single and uniform in size. Incubation was carried out in a water bath at 45 C. for one hour, after which the flasks were placed in the refrigerator and the readings taken the following day.

From the preliminary results obtained with this strain it appears that in the serum of patients with ulcerative colitis there are agglutinins for this strain, and that they are not present to any considerable extent in the serum of healthy persons without intestinal lesions.

Further studies are being carried out on the agglutination test.

TABLE 3.—*Agglutination Tests with Strain 40 Against Patient's Serum*

Patient	Serum Collected	Result of Test with Given Serum Dilution*					
		1:20	1:40	1:80	1:160	1:320	1:640
1.....	12/16/33	++	+	—	—	—	—
1.....	6/ 2/34	+++	++	+	—	—	—
1.....	11/13/34	++++	++++	+++	+	—	—
2.....	1/19/34	++++	++++	+++	—	—	—
3.....	5/12/34	++++	++++	++++	+++	++	+
Miss G., with severe ulcerative colitis.....	11/21/34	++++	++++	+++	+	—	—
Mr. K., with moderately severe ulcerative colitis.....	8/22/34	+++	+	+	—	—	—
Three healthy persons† (control).....	.....	—	—	—	—	—	—
One healthy person (control).....	.....	++	—	—	—	—	—

\* Four pluses indicate complete agglutination; a minus sign, no agglutination. No agglutination occurred in a control tube with antigen and saline solution.

† One of these subjects was Mrs. G., referred to in table 1.

#### COMMENT AND SUMMARY

The isolated colonies of the three patients in whom ileostomies had been performed contained at first many species of organisms in relatively large numbers. In the course of months the flora became largely anaerobic. In all three cases the same type of organism eventually predominated. We have not found a description of this organism in the literature. It closely resembled *Bacteroides fragilis* and *funduliformis* (Thompson and Beaver<sup>5</sup>), *Actinomyces necrophorus* (Shaw,<sup>3</sup> Cunningham<sup>6</sup>) and *Bacillus necrophorus* (Orcutt<sup>7</sup>). There was no zone of clear hemolysis about the colonies on blood agar plates, as described for the aforementioned organisms. A green zone developed about colonies on

5. Thompson, Luther, and Beaver, Donald C.: *M. Clin. North America* **15**: 1611, 1932.

6. Cunningham, John Sumter: *Human Infection with Actinomyces Necrophorus: Bacteriologic and Pathologic Report of Two Cases Terminating Fatally.* *Arch. Path.* **9**:843 (April) 1930.

7. Orcutt, Marion L.: *J. Bact.* **20**:343, 1930.

anaerobic blood agar plates only after exposure to oxygen. This organism was pathogenic to rabbits and, following subcutaneous injections of large amounts of culture, produced local abscesses which tended to heal after a long time. Necrophorus organisms have a tendency to produce spreading lesions, and rabbits subcutaneously inoculated with them often die from six to seven days after the inoculation. Morphologically and culturally the organisms which we have isolated were similar to the necrophorus organisms. In mediums they produced a putrid odor resembling that of butyric acid. They grew well on blood agar and serum dextrose mediums and in dextrose mediums to which a small amount of cystine was added. Exposure to oxygen was highly lethal in a short period.

An organism similar to this predominating anaerobe was isolated from lesions in the large bowels of monkeys. Probably this organism was present in the normal intestinal tract, since it developed in necrotic membranes formed over areas of rectum which were denuded of mucosa. Attempts to isolate it were often unsuccessful in the presence of large numbers of fecal bacteria. It was not found in the healthy isolated colon in two monkeys (CP and TC<sup>6</sup>) or in monkeys with normal colons. Two monkeys fed a culture of this type of organism (strain 11) did not show any symptoms, and in only one case was the organism demonstrated two days after feeding.

Complement-fixing antibodies have been demonstrated in the serum of four patients with ulcerative colitis, using antigen prepared from the predominating anaerobic organism cultured from the isolated colons of two patients. Very slight fixation of complement occurred with an antigen of monkey origin. The serum of one young adult without a history of bowel lesions gave very slightly positive results, whereas the serum of four other healthy young adults gave negative results. The serum taken from one patient (1) gave a negative reaction. This result is difficult to explain in view of the agglutination reactions, which were positive. There was extensive disease of the bowel in the four cases in which the serum gave positive reactions.

The complement-fixation tests with the serum of the three monkeys tested were all positive but in varying degrees. All of these monkeys were subject to previous pathologic disturbance of the large bowel, for an epidemic of the Flexner type of dysentery occurred spontaneously in the colony at about the time this investigation began. The positive result with the serum from monkey 2, taken on July 17, 1934, might be accounted for on such a basis (table 2).

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8. Dack, G. M., and Petran, Elizabeth: Bacterial Activity in Different Levels of Intestine and in Isolated Segments of Small and Large Bowel in Monkeys and in Dogs, *J. Infect. Dis.* 54:205 (March-April) 1934.

Agglutination tests were performed using the serum of five patients with ulcerative colitis against strain 40. Agglutinins were present in all of this serum. The serum from three healthy persons contained no agglutinins for this strain, whereas the serum from a fourth healthy person contained only a trace of agglutinins and then only in the strongest dilution of serum. The agglutination test is being studied more intensively.

Further study is necessary before any definite organism may be considered as the causative agent of ulcerative colitis. Bacteriologic and serologic studies in a larger series of cases of ulcerative colitis may help to evaluate the significance of the organism described in this paper.

## PEPTIC ULCER FOLLOWING EXPERIMENTAL JEJUNOCOLOSTOMY

PAUL E. McMASTER, M.D.

LOS ANGELES

An unexpected and high incidence of "spontaneous" gastric and duodenal ulceration following jejunocolostomy, which was done for studies other than of peptic ulcer, led to an investigation of this unusual and interesting phenomenon, a preliminary report of which has been made.<sup>1</sup>

Numerous methods have been devised whereby acute, subacute and chronic ulceration of the stomach and duodenum can be produced experimentally. Many important observations on the etiology and pathogenesis of peptic ulcer have been made as a result of experimentation on animals. However, I agree with Ivy and Fauley,<sup>2</sup> who stated that there is still much to be learned about this complex problem. The literature on this subject is far too voluminous to summarize in this article. Among some of the more important articles, in which complete bibliographies dealing with this question may be found, are those written by Mann and Williamson,<sup>3</sup> McCann,<sup>4</sup> Ivy and Fauley,<sup>2</sup> Lindau and Wulff,<sup>5</sup> Matthews and Dragstedt,<sup>6</sup> Cushing,<sup>7</sup> Bollman and Mann,<sup>8</sup> Elman and Hartmann,<sup>9</sup> Konjetzny<sup>10</sup> and Steinberg and Proffitt.<sup>11</sup>

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From the Department of Surgery of the University of Chicago.

1. McMaster, P. E.: Experimental Spontaneous Peptic Ulcer, *Proc. Soc. Exper. Biol. & Med.* **30**:126, 1932.

2. Ivy, A. C., and Fauley, G. B.: The Chronicity of Ulcers in the Stomach and Upper Intestine, *Am. J. Surg.* **11**:531, 1931.

3. Mann, F. C., and Williamson, C. S.: The Experimental Production of Peptic Ulcer, *Ann. Surg.* **77**:409, 1923.

4. McCann, J. C.: Experimental Peptic Ulcer, *Arch. Surg.* **19**:600 (Oct.) 1929.

5. Lindau, Arvid, and Wulff, H.: The Peptic Genesis of Gastric and Duodenal Ulcer, *Surg., Gynec. & Obst.* **53**:621, 1931.

6. Matthews, W. B., and Dragstedt, L. R.: The Etiology of Gastric and Duodenal Ulcer, *Surg., Gynec. & Obst.* **55**:265, 1932.

7. Cushing, H.: Peptic Ulcers and the Interbrain, *Surg., Gynec. & Obst.* **55**:1, 1932.

8. Bollman, J. L., and Mann, F. C.: Peptic Ulcer in Experimental Obstructive Jaundice, *Arch. Surg.* **24**:126 (Jan.) 1932.

9. Elman, R., and Hartmann, A. F.: Spontaneous Peptic Ulcers of Duodenum After Continued Loss of Total Pancreatic Juice, *Arch. Surg.* **23**:1030 (Dec.) 1931.

10. Konjetzny, G. E.: Chronische Gastritis und Duodenitis als Ursache des Magenduoodenal Geschwürs, *Beitr., z. path. Anat. u. z. allg. Path.* **71**:595, 1923.

11. Steinberg, M. E., and Proffitt, J. C.: The Etiology of Postoperative Peptic Ulcers, *Arch. Surg.* **25**:819 (Nov.) 1932.

Following the death of two dogs from a perforated duodenal ulcer which developed after the jejunum was sectioned approximately 25 cm. distal to the duodenojejunal junction, both ends being inverted and the proximal stump anastomosed to the colon, it was decided that this occurrence was probably more than merely coincidental. Consequently, studies were designed to determine how often peptic ulceration occurred after jejunocolostomy both with and without retention of the intestine between the points of anastomosis and, if possible, what the etiologic factor might be. In a small series of dogs duodenocolostomy was performed without resecting the intestine between the points of duodenal transection and anastomosis into the colon.

Experimental procedures and observations similar to these were not found recorded in the literature.

#### METHOD

All operations were performed on healthy adult dogs under anesthesia induced by morphine and ether, with an aseptic technic. Through a right paramedian incision the jejunum was isolated and transected approximately from 20 to 30 cm. distal to the duodenojejunal junction. Both ends of the cut jejunum were inverted with a purse-string suture. A side-to-side anastomosis was then made between the proximal jejunal stump and the ascending colon (fig. 1 *A*). Twenty dogs were used in this series.

In a second series of eleven dogs the jejunum was exposed and sectioned as in the preceding group. The end of the proximal jejunal stump was closed by a purse-string suture, and the rest of the jejunum, all of the ileum and the appendix and the cecum were then excised. The cut end of the stump of the colon was invaginated, and a side-to-side anastomosis was made between the remaining upper part of the jejunum and the colon (fig. 1 *B*).

At no time during the operative procedure was the stomach, the duodenum or the upper part of the abdomen handled or explored in the two series of experiments, thus eliminating the element of trauma to these parts.

Duodenocolostomy was performed on a third series of three dogs. In these experiments the duodenum was sectioned approximately 10 cm. distal to the pylorus; both ends were inverted and an anastomosis was made between the proximal duodenal stump and the colon (fig. 1 *C*). The part of the intestine distal to the point of the duodenal section was left *in situ*.

For the first three postoperative days all the animals were given only physiologic solution of sodium chloride intravenously. Fluids and solid foods were then given by mouth in gradually increased amounts until the stock diet was being fed.

In addition to observations on the occurrence of peptic ulcer following jejunocolostomy, some studies of the blood chemistry were made. These included determinations of cholesterol, sugar, calcium, nonprotein nitrogen and chlorides which were made just before operation and at irregular intervals during the experiments. The weight was recorded throughout the experiments.

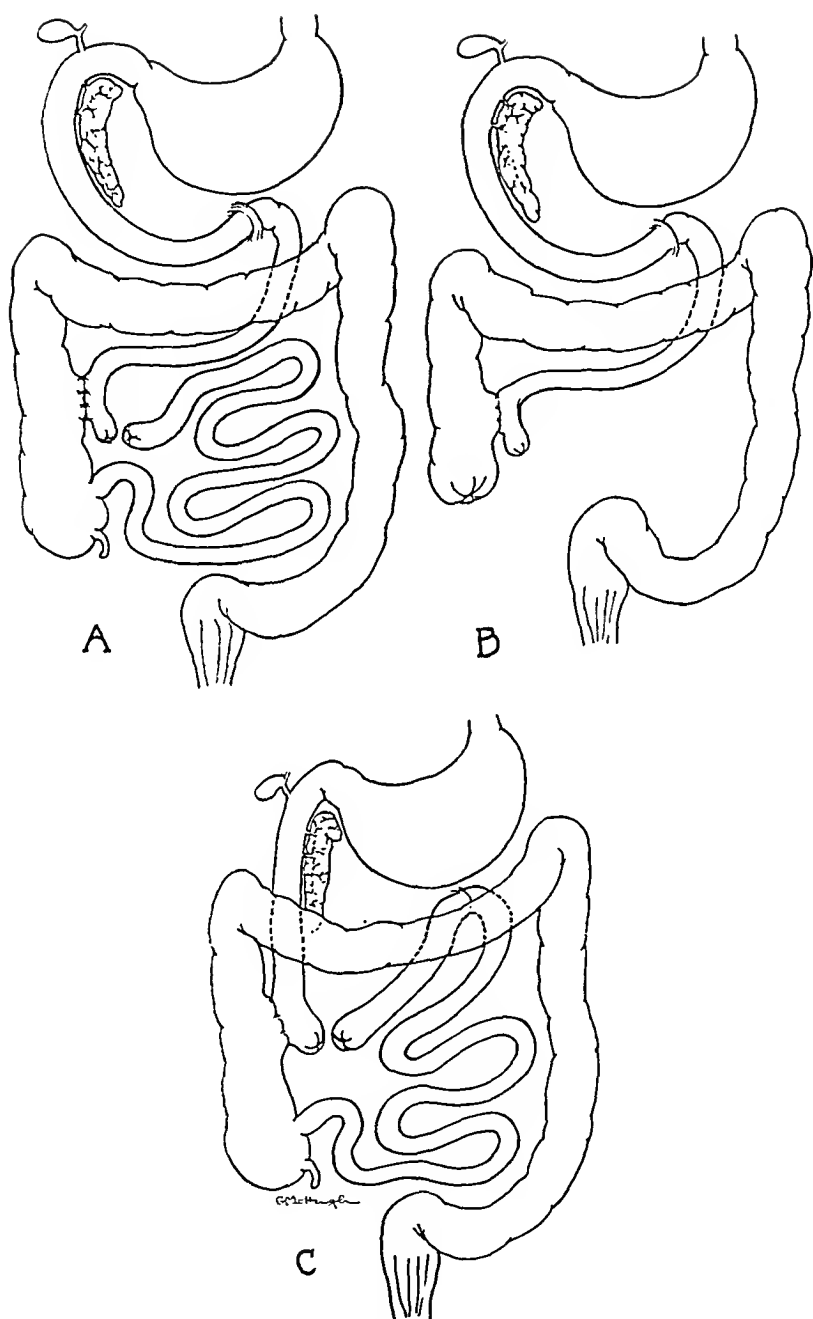


Fig. 1.—*A* is a diagrammatic representation showing jejunocecalostomy in which the average distance between the pylorus and the point of jejunal section was 49 cm., and the average length of intestine between the point of section and the ileocecal valve was 278 cm. *B* shows jejunocecalostomy in which the average distance from the pylorus to the point of jejunal section was 54 cm. and the average length of intestine resected was 254 cm. *C* shows duodenocolostomy in which the average distance from the pylorus to the point of duodenal section was 10 cm. and the average length of intestine from the point of section to the ileocecal valve was 291 cm.



## RESULTS

*Jejunocolostomy Without Resection of the Intestine Between the Point of the Jejunal Section and the Anastomosis of the Colon.*—Of the twenty dogs in this series, in thirteen, or 65 per cent acute, subacute or chronic peptic ulceration developed (fig. 2). Three of the ulcers perforated the wall of the intestine and caused death from peritonitis (figs. 3 and 4). Most of the animals lost con-



Fig. 2.—Photograph showing multiple acute erosions and ulceration of the prepyloric mucosa, present five days after jejunocolostomy. The distal portion of the small intestine was not excised and remained as a blind stump.

siderable weight, and two at death weighed less than half of their preoperative weight. Both of these had peptic ulcers. Two others that lost practically half of their preoperative weight showed no ulcer of the stomach or duodenum. The average length of life of the dogs in this series was twenty-three days; however, some were killed while in fairly good condition. The shortest time a dog lived

was five days. The longest was one hundred and forty-four days, and at the end of that time the dog was killed. Despite the fact that he had lost considerable weight, his general condition seemed good, and the finding of a large chronic duodenal ulcer which was healing was somewhat unexpected. The average distance from the pylorus to the point of jejunal section in this series was 49 cm. (fig. 5), and the average amount of "short circuited" intestine, or the distance from the point of jejunal section to the ileocecal valve, was 278 cm. The results obtained in this series are shown in table 1.



Fig. 3.—Photograph showing a large perforated duodenal ulcer and a subacute prepyloric ulcer, present forty-three days after jejunocolostomy. The distal portion of the small intestine was not excised. The dotted line indicates the pylorus.

*Jejunocolostomy with Resection of the Distal Portion of the Jejunum and All of the Ileum, Appendix and Cecum.*—Eleven dogs were used in this series, and peptic ulceration developed in only two, giving an incidence of 18 per cent. One of the dogs showed acute erosions of the gastric mucosa, and another showed both acute and subacute lesions. The dog in this series which survived the longest lived for ninety-four days and lost nearly 60 per cent of his preoperative weight, but peptic ulceration did not occur. The shortest length of time a dog

in this series lived was ten days, and the average for the eleven dogs was thirty-four days. Each of the animals in whom peptic lesions developed weighed at death only half of the preoperative weight. Four others that lost practically as much weight showed no peptic ulceration.

The dogs ate well but showed a gradually increasing loss of weight. Only when the condition which caused death set in did anorexia develop. Diarrhea was noted occasionally but for the most part was not a conspicuous symptom.



Fig. 4.—Photograph showing a large perforated duodenal ulcer, present thirty-seven days after jejunocolostomy. The distal portion of the small intestine was not excised. The dotted line indicates the pylorus.

The longest segment of intestine resected in any animal measured 326 cm. and the shortest 132 cm. The average length was 254 cm., and the average distance from the pylorus to the point of jejunal severance was 54 cm., corresponding with that portion of the small intestine through which food passed before entering the colon. In two of the experiments studies of the blood chemistry were made, and

no essential changes were found in the amount of cholesterol, sugar, calcium chlorides or nonprotein nitrogen. The results obtained in this series are shown in table 2.

*Duodenocolostomy Without Resection of the Intestine Distal to the Proximal Duodenal Section.*—In three dogs subjected to this operation peptic ulceration did not occur. The average length of intestine between the point of duodenal excision



Fig. 5.—Photograph showing a large subacute prepyloric ulcer. The point of jejunal section (A) was 38 cm. distal to the pylorus (dotted line). The anastomosis of the jejunum to the proximal ascending colon is shown at C. The distal jejunum of the small intestine was not excised.

which was approximately 10 cm. distal to the pylorus, and the ileocecal valve was 291 cm. Twenty-three days was the average postoperative length of life of these dogs. In one the loss of weight was 50 per cent, while in the other two it was less. The results obtained in this series are shown in table 3.

TABLE 1.—*Jejunocolostomy Without Resection of Intestine*

Dog	Jejunal Section Distal to Pylorus, Cm.	Jejunal Section Proximal to Ileocecval Valve, Cm.	Length of Experiment, Days	Autopsy Observations	Pre-operative Weight, Kg.	Weight at Death, Kg.	Peptic Ulceration
275	53	216	7	Intussusception .....	14	11.6	0
243	60	210	144	Large, chronic duodenal ulcer, pneumonia	12	7.5	+
282	71	360	43	Peritonitis; perforated duodenal ulcer and one subacute gastric ulcer	16.8	6.8	+
223	45	300	40	No peptic ulcer; three large acute ulcers of the colon	13.6	7	0
226	36	245	39	Gastric ulcer; walled off, perforated duodenal ulcer	11.6	5.2	+
473	61	500	7	Duodenal mucosal hemorrhages; no ulcers; had diarrhea with huge quantities of blood	23	18	0
474	58	395	5	Peritonitis; anastomotic leak....	21.2	19	0
476	38	222	26	Two gastric ulcers; one acute and one subacute	9.4	5.1	+
471	43	302	14	Acute gastric ulceration.....	9.9	5.1	+
527	100	350	8	Acute prepyloric ulcers; pneumonia	33.2	25.8	+
530	30	212	8	Pneumonia .....	9.7	6.1	0
525	38	255	16	No peptic ulcers; pneumonia....	9	4.5	0
562	38	235	18	Multiple gastric erosions; one duodenal and one prepyloric ulcer	9	5.4	+
576	39	246	12	No ulcers; cachexia.....	6.4	3.9	0
575	41	252	9	Pneumonia; acute gastric erosions	8.8	6	+
572	41	230	16	Infection in skin wound; many acute gastric erosions	8.8	5	+
597	40	260	37	Perforated duodenal ulcer; peritonitis	7.9	4.2	+
659	43	260	35	Pneumonia; subacute and acute peptic ulceration	8.3	4.2	+
649	38	230	5	Pneumonia; acute ulcers of the stomach	9	5	+
220	60	250	50	Killed; multiple acute gastric ulcers	17.4	9	+

TABLE 2.—*Jejunocolostomy with Resection of the Distal Portion of the Jejunum, and the Ileum, Appendix and Cecum*

Dog	Jejunal Section Distal to Pylorus, Cm.	Intestine Resected, Cm.	Length of Experiment, Days	Autopsy Observations	Pre-operative Weight, Kg.	Weight at Death, Kg.	Peptic Ulceration
701	48	295	94	Cachexia; no ulcers; no pneumonia	18.4	8.8	0
702	63	275	11	Pneumonia .....	11.2	6.2	0
660	69	325	56	Perforated jejunal anastomotic ulcer associated with silk worm gut suture; multiple acute gastric erosions	25	13.8	+
696	36	132	19	Pneumonia; no ulcers.....	9.6	6	0
715	45	280	10	Distemper; no ulcers.....	12.4	9	0
692	50	175	11	Peritonitis; anastomotic leak; no ulcers	8	6	0
732	60	315	14	Distemper; no ulcers.....	21	14.2	0
767	54	292	45	Perforated jejunal ulcer associated with silk worm gut suture; no peptic ulcers	17.4	10.8	0
644	55	190	57	Cachexia; no ulcers.....	6	3	0
838	68	326	45	Early stages of pneumonia; three acute gastric ulcers	24.2	12.2	+
848	64	285	17	Pneumonia; no ulcers.....	21.8	14.2	0

TABLE 3.—*Duodenocolostomy Without Resection of Intestine*

Dog	Duodenal Section Distal to Pylorus, Cm.	Duodenal Section Proximal to Ileocecval Valve, Cm.	Length of Experiment, Days	Autopsy Observations	Pre-operative Weight, Kg.	Weight at Death, Kg.	Peptic Ulceration
281	9	328	22	Pneumonia; no irritation of the colon; no ulcers	13.5	8	0
227	9	240	28	Emaciated; no irritation of the colon; no ulcers; cause of death (?)	7	3.5	0
274	10	305	18	Pneumonia; no ulcers.....	10	6.5	0

## COMMENT

In a study of microscopic sections from the various peptic lesions which were found in the foregoing experiments all stages of ulceration were noted. These ranged from early stages of acute erosions, of which some extended to the muscularis mucosae and others involved only the superficial mucosae, with a slight surrounding inflammatory reaction, to typical chronic ulcers with punched-out borders and deep bases. A few had perforated the intestinal wall. Practically all of the lesions were associated with chronic inflammation and lymphocytic infiltration of the surrounding muscularis. This condition was slight in the acute lesions but became progressively more intense as the severity and chronicity of the ulceration increased. This observation does not seem to substantiate the work of Konjetzny,<sup>10</sup> who expressed the belief that chronic gastritis and duodenitis were the predisposing cause of peptic ulceration. The amount of inflammatory reaction in the stomach and duodenum associated with the peptic ulceration in the preceding experiments seemed to follow, and be in direct proportion to, the age and chronicity of the ulcerations rather than to precede the onset of the acute lesions.

It is of interest to note that in some of the animals multiple lesions were found which exhibited different stages of ulceration, ranging from acute erosions to more chronic ulcers (fig. 6). This suggests that acute erosions or ulcerations may lead to chronic peptic ulcers, although Spira<sup>12</sup> stated that this does not occur.

No definite etiologic factor seems apparent to explain why the peptic ulcers formed "spontaneously." If the upper part of the abdomen had been explored, the stomach or duodenum traumatized or handled or some disturbance produced in the bile or pancreatic ducts in such a way that the secretions were diminished or eliminated, a more definite explanation might be propounded. But in the absence of any of these factors other causes must be considered.

It has been suggested by some authors that loss of weight and decreased resistance with resultant cachexia might lead to peptic ulceration. This hardly seems tenable in the light of the present experiments, for if this were true why did the dogs with extensive intestinal resections, in each of whom there was a marked loss of weight, show an incidence of ulceration of only 18 per cent while the dogs on whom the same operation was performed except that the intestine was left in situ showed an incidence of 65 per cent? Also, in the three experiments of duodenocolostomy in which the dogs lost considerable weight, ulcera-

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12. Spira, J. J.: *The Causation of Chronic Gastro-Duodenal Ulcers*, New York, Oxford University Press, 1931.

tion in the stomach or duodenum did not occur. Hence it does not seem that severe loss in weight or cachexia is the sole explanation.

At autopsy, in the animals in which the small intestine was not excised, there was found in the lumen of the ileum an "inspissated, thick, yellow, cheesy material." Some of this substance was like food which might have been regurgitated through the ileocecal valve and

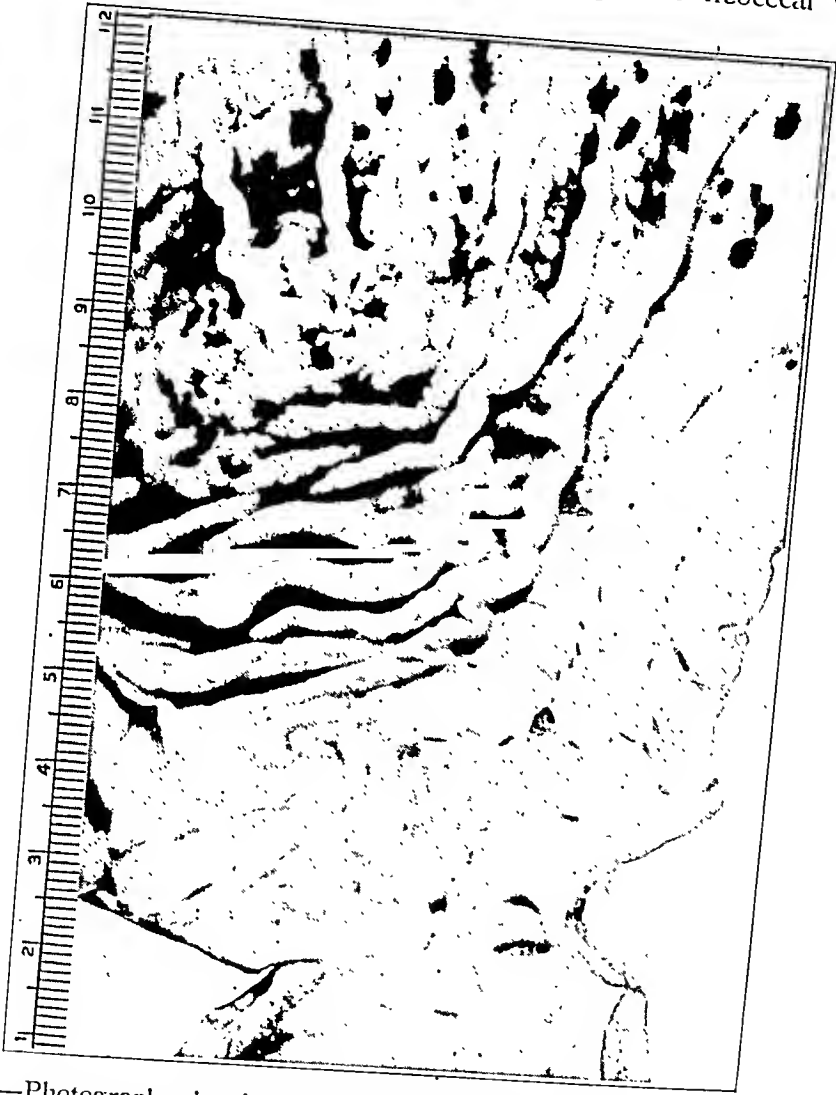


Fig. 6.—Photograph showing mucosal hemorrhages in the fundus of the stomach. Multiple erosions, acute ulcerations and also a rather large subacute ulcer in the prepyloric region were present eighteen days after jejunocolostomy. The distal portion of the small intestine was not excised.

carried up the intestinal tract by reverse peristalsis. The other portion of this material was apparently excretory and secretory products from the intestinal canal. The impression obtained from observing this substance was that normal intestinal peristalsis, especially in the lower part of the ileum, had been greatly altered and a condition of intestinal stasis

had resulted. As it was thought that this factor might possibly decrease the normal gastric emptying time, thus exposing the mucosa of the stomach to the acid gastric contents for a longer time and predisposing it to peptic ulceration, comparative fluoroscopic studies of several animals, with and without resections of the intestine, were made pre-operatively and at irregular postoperative intervals. The results were somewhat inaccurate owing to technical difficulties, but in a few observations which appeared fairly accurate there were no pronounced changes in the emptying time of the stomach.

Owing to the decrease in the absorptive space of the bowel in these experiments, essential organic or inorganic substances probably passed through the shortened intestinal tract without being assimilated. Dalldorf and Kellog<sup>13</sup> noted gastric ulcers developing in albino rats fed diets deficient in vitamin B. The possibility of deficiency in some vitamin influencing the occurrence of peptic ulceration in the aforementioned experiments is only an interesting speculation. No definite observations giving results either for or against this possibility were made.

As the greatest incidence of gastroduodenal ulceration occurred in the animals in which the intestine had not been resected, this portion of the intestine seems to be the most logical place to look for the etiologic factor. With a condition of "stasis" present in the remaining "inactive" small intestine the likelihood of bacteria or toxins being absorbed and influencing peptic ulceration must be considered. Rosenow<sup>14</sup> in his work on the causation of peptic ulcer considered foci of infection important. He mentioned that among the many foci the intestinal tract, which for mechanical reasons can neither drain nor heal well, should be regarded as a test tube with permeable walls embedded in the tissues. He has been able to demonstrate in stained sections of the intestine the presence of streptococci in the tissues surrounding the peptic ulcer. Also by cultures of fresh specimens from ulcers, he has isolated these bacteria, which when injected into experimental animals have caused peptic ulceration. Neither cultures of the ulcers in the foregoing experiments nor stains of microscopic sections for the presence of these bacteria were made.

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13. Dalldorf, G., and Kellog, M.: Incidence of Gastric Ulcer in Albino Rats Fed Diets Deficient in Vitamin B ( $B_1$ ), *J. Exper. Med.* **56**:391, 1932

14. Rosenow, E. C.: The Production of Ulcer of the Stomach by Injection of Streptococci, *J. A. M. A.* **61**:1947 (Nov. 29) 1913. The Causation of Gastric and Duodenal Ulcer by Streptococci, *J. Infect. Dis.* **19**:333, 1916. Focal Infections and Elective Localization of Bacteria in Appendicitis, Ulcer of the Stomach, Cholecystitis and Pancreatitis, *Surg., Gynec. & Obst.* **33**:19, 1921. Focal Infection and Elective Localization, *Internat. Clin.* **2**:29 (June) 1930.



## SUMMARY

Following jejunocolostomy in which the distal portion of the jejunum and the ileum were left in situ as a blind stump, acute, sub-acute or chronic peptic ulceration was noted in thirteen, or 65 per cent, of twenty dogs operated on. Three of the ulcers perforated the wall of the intestine, leading to peritonitis. In three dogs on which duodenocolostomy was performed, leaving the distal portion of the duodenum, the jejunum and the ileum as a blind stump, peptic ulceration was not noted.

When a jejunocolostomy was performed with resection of the intervening bowel, peptic ulceration occurred in two, or 18 per cent. of eleven dogs operated on.

A rather marked loss of weight occurred in nearly all of these animals, but this did not seem to be the etiologic factor responsible for the peptic ulcers.

Gastritis and duodenitis, as evidenced by inflammatory reaction in the surrounding walls of the stomach and duodenum, seemed to follow rather than precede the peptic ulceration, as nearly as could be determined by microscopic studies.

1930 Wilshire Boulevard.

# INFECTIOUS GANGRENE OF THE SKIN DUE TO BACTERIAL SYNERGISM

WITH PARTICULAR REFERENCE TO NOMA AND POSTOPERATIVE  
CUTANEOUS GANGRENE

N. FREDERICK HICKEN, M.D.

OMAHA

Gangrenous infections of the skin and subcutaneous tissues are much more common than is usually appreciated. These necrotizing processes develop rapidly, destroying the involved tissues and jeopardizing the lives of the patients. Fusospirochetal, amebic and streptococcic infections, ecthyma, gas gangrene and phagedenic ulcers of the thoracic and abdominal walls following operations for suppurative processes are the most common clinical expressions of bacterial gangrene of the skin.

Accurate diagnosis and scientific treatment depend on the identification of the invading organisms as well as on an appreciation of the local tissue reaction and the systemic response to such infections. Meleney<sup>1</sup> maintained that complete bacteriologic studies, employing anaerobic as well as aerobic methods, are necessary if one expects to isolate the provocative organisms. Cultures should be made from biopsy specimens taken from various areas of the lesion. By such painstaking bacteriologic examination, he has demonstrated that a bacterial synergism, or a symbiotic relationship between certain bacteria, is responsible for these gangrenous lesions.

Recently I have seen two patients with such conditions: one had a gangrenous stomatitis (noma) associated with acute myelogenous leukemia, and the other had a large sloughing necrotic ulcer of the thoracic wall following a thoracotomy for empyema. Both lesions were very destructive. They spread rapidly and produced severe systemic reactions similar to those seen with virulent bacterial infections. Bacteriologic and experimental studies indicated that both lesions were due to bacterial synergism and hence were of sufficient interest to merit reporting.

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## A CASE OF NOMA

*History.*—A Negro boy, aged 3, was admitted to the University of Nebraska Hospital because of a "sore mouth."

He was well until three weeks prior to admission, at which time his ankles, wrists and right shoulder were painfully swollen. Examination at the dispensary revealed enlargement and congestion of the tonsils, diffuse bilateral cervical adenopathy, and inflammatory periarticular swelling of the hands, feet and ankles. Within two weeks' time the "rheumatic pains" had subsided and the boy felt well. Apparently he had had mild inflammatory arthritis, which was thought to be related to the tonsillar infection; therefore, a tonsillectomy was advised just as soon as his general condition permitted. Unfortunately no hematologic studies were made at the dispensary.



Fig. 1.—The gangrenous noma has perforated the cheek. Note the induration and inflammatory swelling surrounding the ulcerative area.

A week later while chewing gum he bit the inner surface of the right cheek. Within two days, the entire cheek was swollen, tender and painful. He refused to eat. His breath became offensive. Four days after the original trauma, his mother noticed a large sloughing ulcer on the inner surface of the right cheek. Hot packs and irrigations of the mouth merely aggravated the condition, so the child was returned to the dispensary.

*Physical Examination.*—The patient was a well nourished Negro boy with a temperature of 101.3 F.; his pulse rate was 120 beats per minute; his respirations were 18. The right cheek, the right side of the nose and both lips were swollen, firm and hyperemic. On the inner surface of the cheek was a large sloughing ulcer which was covered with a gray necrotic membrane. This membrane was easily removed, leaving a dark nonbleeding ulcer base. The ulcer not only had spread peripherally but had directly invaded the soft tissues of the cheek. The

gums were swollen and tender but presented no areas of ulceration, necrosis or bleeding. The tonsils were enlarged, and plugs of inspissated material could be expressed from the tonsillar crypts. The breath had a repulsive fetid odor.

The cervical lymph nodes were hypertrophic, firm, fixed and discrete, but not tender. The inguinal, axillary, epitrochlear and popliteal nodes were small, firm and "shotlike." The liver extended 1 fingerbreadth below the costal margin; it was smooth, moved with respirations and was not tender. The spleen could not be palpated.

According to the blood count on admission, there were 5,200,000 erythrocytes, with a hemoglobin percentage of 73. There were 44,500 leukocytes, with a differential count of 43 per cent polymorphonuclear segmented cells, 10 per cent staff forms, 12 per cent young forms, 5 per cent myelocytes, 1 per cent promyelocytes, 2 per cent blast cells, 10 per cent lymphocytes, 15 per cent monocytes and 2 per cent unidentified forms. Forty-four nucleated and other immature red cells were seen while the white cell count was being made. Fifty-nine per cent of the leukocytes gave a positive oxidase reaction. Apparently the child had acute myelogenous leukemia complicated by ulcerative stomatitis.

*Treatment and Course.*—Active therapy consisted of intramuscular injections of nearsphenamine, irrigations of the oral cavity with oxidizing solutions such as potassium permanganate and sodium perborate, and applications of moist and dry heat every three hours. Repeated transfusions of whole blood were given in an attempt to stimulate his defensive mechanism.

In spite of these therapeutic attempts, the ulceration spread rapidly; his condition became very toxic; his pulse rate increased to 130 beats per minute, and his temperature varied from 100 to 101.8 F. After two weeks the right side of his face was intensely swollen, and the brawny induration had increased. The skin overlying the central portion of the inflammatory tumor had a peculiar brownish discoloration; it rapidly became black and gangrenous, and finally the ulcer perforated. This large, foul-smelling, perforating ulcer, which permitted the constant drooling of saliva, combined with the extensive inflammatory swelling of the face presented a most gruesome sight.

On the thirty-ninth day of his stay in the hospital the patient was seen in surgical consultation, and I felt that even in the presence of leukemia the necrotizing ulcer should be excised. This would not materially influence the course of the leukemia, but removal of the gangrenous, decomposing tissue with its resultant infection would make nursing care more pleasant and reduce the absorption toxemia.

Under avertin narcosis, all the diseased tissue, which constituted the right cheek and part of the upper and lower lips, was removed by cautery excision. The periosteum and the cortical portion of the maxilla were diseased, and this infected tissue was removed with a curet. Hot fomentations and frequent irrigations soon stimulated the growth of healthy granulation tissue.

The child made an excellent response until the ninth postoperative day. He then contracted an epidemic streptococcal sore throat and laryngitis which finally terminated in bilateral bronchopneumonia. He seemed unable to combat this widespread systemic infection, for his resistance was very low. Seventeen days after the first operation, it was necessary to excise a portion of the necrotic gingival tissue from the maxilla and mandible and to extract four teeth. The infected bone was removed by curettement. The ulceration, however, continued, and for a third time the diseased portions of the cheek and lip were removed. During the remainder of his hospitalization there was no recurrence of theomatous process.



Fig. 2.—Appearance of the face after excision of the noma. The mucous membrane is rapidly covering the denuded areas.



Fig. 3.—Acute streptococcic dermatitis of the ear, face, neck and trunk. Non-hemolytic streptococci were recovered from the vesicular fluid. There was no evidence of preexisting noma.

On the twenty-second postoperative day a small vesicle appeared on the inner surface of the left external ear. In five hours the entire ear was covered with a large "blister." The epidermis was separated from the dermis by a clear yellow fluid. When the top of the vesicle was removed, the dermis appeared very red and hyperemic and was very painful. No ulceration, necrosis or gangrene was seen. Within two days' time the inflammatory process had practically subsided. Three days later a similar bleb appeared in the suprasternal notch, and after six hours it had completely covered the right side and posterior portions of the neck. The epidermis seemed to float on top of this yellow serous exudate, from cultures of which grew nonhemolytic streptococci. Five days later several small vesicles developed in the interscapular area, became confluent and quickly encircled the entire trunk. Nonhemolytic streptococci were recovered from this vesicular fluid. Careful examination did not reveal any abscesses, necrosis or gangrene of the dermal tissues.

The child died on the thirtieth postoperative day from acute myelogenous leukemia, bronchopneumonia and acute streptococcic dermatitis. There was no evidence of the preexisting noma; in fact, the oral mucosa was rapidly covering the denuded areas.

#### COMMENT

Noma is a progressive gangrenous ulcer, usually involving the oral cavity. However, it may affect any part of the body. For example, Pollard<sup>2</sup> observed a "nomatous ulcer" of the leg. Henoch<sup>3</sup> described a similar lesion of the vulva and labia. Holt<sup>4</sup> reported seven instances in which the "noma" originated in the external auditory canal or the middle ear, where it had been superimposed on long-standing otitis media. Noma is usually seen as a complication of measles, typhoid fever, scarlet fever, diphtheria, pneumonia or leukemia; in fact, any disease which materially lowers the resistance of the host may be a precursor of this malady. Portmann<sup>5</sup> observed a case of noma which occurred spontaneously without any preceding infection, but this is very unusual.

The destructive nature of noma has caused it to be confused with malignant lesions, for it has been frequently referred to as "cancrum oris," "water cancer," "scorbutic cancer," etc. Since the advent of bacteriology, numerous organisms have been recovered from these gangrenous lesions, each one of which has been thought to be the causative factor. The fusiform bacillus, the spirochete, the streptococcus, the staphylococcus, the streptothrix, the cladothrix and the

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2. Pollard, quoted by Weaver, G. H., and Tunnicliff, R.: *Wien. klin. Wchnschr.* **18**:1236, 1905.

3. Henoch, E.: *Vorlesungen über Kinderkrankheiten*, Berlin, A. Hirschwald, 1890, p. 464.

4. Holt, L. E.: *Diseases of Infancy and Childhood*, ed. 10, New York, D. Appleton & Company, 1920.

5. Portmann: Noma Arising Spontaneously, cited in Kauffman, Edward: *Pathology for Students and Practitioners*, translated by P. Reimann, Philadelphia, P. Blakiston's Son & Company, 1929, vol. 1, p. 552.

diphtheria bacillus have been the most frequent invaders. Vincent<sup>6</sup> maintained that the spirochete and the fusiform bacillus were the provocative agents. Sobel and Hermann<sup>7</sup> believed that the fusiform bacillus and the spirochete were the same organism in different phases of development. Weaver and Tunnicliff<sup>8</sup> and Rona<sup>9</sup> thought the fusiform bacillus to be the etiologic agent and the spirochete merely an incidental invader. Walsh<sup>10</sup> studied eight cases of noma and felt that the diphtheria bacillus was responsible for the necrotic ulceration. Ranke,<sup>11</sup> Holt<sup>4</sup> and Verhoeff<sup>12</sup> maintained that the streptococcus was the most important pathogenic factor. Great difficulty was encountered in determining which organisms were responsible for the actual death and disintegration of the tissues and which were merely incidental invaders. Many bacteria escaped detection because anaerobic cultures were not made. Thus the pathogenicity of noma remains an open question.

With the hope of shedding some light on this problem, Dr. P. M. Bancroft of the department of bacteriology made anaerobic and aerobic cultures on many different mediums from pieces of tissue taken for biopsy from various portions of the nomatous ulcer. From the surface of the ulcer itself, he recovered fusiform bacilli, spirochetes, nonhemolytic streptococci, *Staphylococcus aureus*, diphtheroid bacilli and many gram-negative bacilli. From a small piece of tissue excised from the zone of reaction, he obtained growth of pure strains of anaerobic microaerophilic nonhemolytic streptococci, anaerobic fusiform bacilli and anaerobic *Staph. aureus*. Both the streptococci and the staphylococci grew in aerobic conditions also. All anaerobic cultures were grown in a vacuum tank in which the proper tension and concentration of carbon dioxide and hydrogen could be maintained. Mixed cultures of the three latter organisms presented the same offensive fetid odor as did the nomatous lesion of the patient.

Microscopic studies of the gangrenous ulcer confirmed the bacteriologic findings and demonstrated three distinct types of reaction to this infection. In the gangrenous area, all tissues had become necrotic, losing their morphologic characteristics. The cell nuclei were pyknotic

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6. Vincent, H.: Sur l'étiologie et sur les lésions anatomopathologiques de la porriture d'hospital, *Ann. Inst. Pasteur* 10:488, 1896.

7. Sobel, J., and Hermann, Charles: Ulceromembraneous Angina Associated with Fusiform Bacilli (Vincent): Report of Twelve Cases in Children, *New York M. J.* 74:1037 and 1043, 1901.

8. Weaver, G. H., and Tunnicliff, R.: Noma, *J. Infect. Dis.* 4:8, 1907.

9. Rona: *Arch. f. Dermat. u. Syph.* 67:259, 1903.

10. Walsh: *Proc. Path. Soc., Philadelphia* 4:179, 1901.

11. Ranke, quoted by Weaver, G. H., and Tunnicliff, R.: *München med. Wchnschr.* 47:1485, 1900; 49:1787, 1902; 50:13, 1903.

12. Verhoeff, F. H.: *J. Boston Soc. M. Sc.* 5:461, 1900.

and fragmented, the cell walls had disintegrated, and the entire mass of necrotic tissue stained homogeneously. In the zone of reaction a very different condition prevailed. The walls of the blood vessels were slightly thickened, and their lumens were plugged with obstructing thrombi. As one approached the normal tissue the lumens of the vessels were patent but contained clumps of degenerating erythrocytes. Scattered throughout the zone of reaction were rod-shaped bacilli with rounded ends. They had invaded the skin and subcutaneous tissues and were either clumped together or arranged in a palisade formation. Isolated groups and short chains of cocci were frequently seen, some of which had been engulfed by polymorphonuclear phagocytes. In the marginal zone—the junction of the normal and diseased tissue—there was a mild inflammatory reaction; all tissues were hyperemic, and the blood vessels were engorged; there was some polymorphonuclear infiltration but no leukemic change.

As these studies failed to show any evidence of leukemic infiltration it was apparent that the noma-like ulcer was due to an active bacterial infection. The bacterial toxins and products, combined with the thrombosis of the blood vessels, accounted for the necrosis and devitalization of the facial tissues. The presence of a mixed infection suggested the possibility of bacterial synergism, so the following experimental studies were made.

#### EXPERIMENTAL DATA

If noma is an infective bacterial gangrene, what are the provocative micro-organisms?

As previously stated, anaerobic and aerobic cultures were made from the surface of the gangrenous and necrotic areas, from which non-hemolytic streptococci, *Staph. aureus*, pneumococci, diphtheroid bacilli and unidentified gram-negative bacilli were isolated. In order to determine the pathogenicity of these organisms, animal inoculations were made. One cubic centimeter amounts of a suspension of the nonhemolytic streptococci in physiologic solution of sodium chloride were injected into the abdominal skin of rabbits and guinea-pigs. Similar procedures were carried out with each of the other organisms. The nonhemolytic streptococci caused a mild local dermatitis which completely subsided within forty-eight hours. *Staph. aureus* produced a small subcutaneous abscess with a mild inflammatory dermatitis, both reactions disappearing after four days. The guinea-pigs seemed much more sensitive to these injections than the rabbits. Suspensions of pneumococci, diphtheroid bacilli and gram-negative bacilli each failed to initiate any dermal reaction. These organisms were then used in various combinations, and only a very mild localized dermatitis resulted, with no evidence



of ulceration, necrosis or gangrene at the sites of injection. Furthermore, when a mixed suspension of all these bacteria was injected into the abdominal skin of these laboratory animals, only a mild cutaneous reaction occurred. Thus we were unable to reproduce a "noma-tous-gangrene" by the intracutaneous injection of either a pure or a mixed bacterial suspension of the organisms found on the surface of the necrotic facial ulcer.

Since we had failed to isolate the causative bacteria from the surface of the gangrenous process, it became evident that the inciting organism might be confined to the tissues at the margin of the advancing inflammatory lesion. Under strict aseptic precautions, small pieces of tissue were removed from the zone of reaction, and both anaerobic and aerobic cultures made. Anaerobic micro-aerophilic nonhemolytic streptococci, fusiform bacilli and anaerobic and aerobic *Staph. aureus* were found in abundance. No diphtheroid bacilli, gram-negative bacilli or pneumococci were found, indicating that these were merely incidental surface invaders of the gangrenous tissues. In attempting to reproduce the noma, 1 cc. amounts of a suspension of fusiform bacilli in physiologic solution of sodium chloride were injected intracutaneously into the guinea-pigs and rabbits. Repeated attempts failed to elicit even the slightest tissue response. Similar injections of anaerobic nonhemolytic streptococci resulted in an evanescent localized dermatitis. The staphylococci produced small subcutaneous abscesses, but no ulceration appeared. Combinations of any two of these organisms caused only mild inflammatory reactions of the skin. In no instance was there tissue destruction or necrosis.

A mixed bacterial suspension consisting of the fusiform bacilli, the staphylococci and the nonhemolytic streptococci was now introduced into the skin of the test animals. Within twenty-four hours' time there was a pronounced local tumefaction. The skin became inflamed, hyperemic and very tender. At the end of seventy-two hours, the hyperemic tumors measured 3 cm. in diameter, and the overlying skin had acquired a brownish hue. The tumor mass did not fluctuate. Within ninety-six hours a small ulceration measuring 2 mm. in diameter appeared at the site of injection. Its borders were sharply demarcated, giving it a punched-out appearance. During the next twenty-four hours the ulcer spread until it measured 2.5 cm. in diameter. Its margins were black and gangrenous, the skin and subcutaneous tissues were undermined, and the fascia overlying the abdominal muscles was destroyed. No bleeding occurred from small incisions made into the borders of the ulcer. The tissues were edematous and indurated. The necrotizing ulcer rapidly increased in size until it measured 5 cm. in diameter. It then seemed to remain stationary for five days. The general appearance of the animal improved, signs of tissue repair appeared.

and within two weeks' time the lesion had completely healed. The rabbits seemed more resistant to these infections as only very small ulcerations appeared at the sites of injection, and these healed rapidly.

Microscopic studies of the ulcer tissue from the guinea-pig revealed a much more fulminating process than was present in the patient's ulcer. Considerable leukocytic infiltration, areas of abscess formation, marked hyperemia and congestion of all tissues were seen. Groups of cocci had been phagocytosed by the polymorphonuclear cells. In the gangrenous areas the morphologic characteristics of all dermal structures had been destroyed.

From these experimental studies, it is apparent that the nomatous ulcer was due to a bacterial synergism between the fusiform bacilli, the anaerobic nonhemolytic streptococci and *Staph. aureus*. Individually these organisms were incapable of reproducing the noma, but combined they effected a rapidly progressing phagedenic ulcer which completely destroyed the involved tissues. Of course, one must always view animal experimentation with reservation, but such studies as these are more than suggestive, for they present strong evidence that noma is caused by bacterial symbiosis.

This concept is further corroborated by other clinical observations. Remember that this patient had two dermal lesions, one a true nomatous ulcer and the other a streptococcic dermatitis. This streptococcic infection was extremely virulent, rapidly destroying the epidermis and evoking a pronounced hyperemia of the dermis with resultant serous effusion. Nonhemolytic streptococci were isolated from both lesions. Why, then, did not the areas of dermatitis actively infected with streptococci undergo gangrenous changes? The patient's general condition favored a nomatous development, for such a lesion had already been produced. Why did not noma develop in these large denuded areas of dermatitis? Simply because the streptococcus alone could not produce a noma. Remember, then, that when injected intradermally into animals, the streptococci did not produce necrosis of tissue but merely a localized dermatitis. It evidently required the symbiotic relationship between the anaerobic nonhemolytic streptococci, the fusiform bacilli and the staphylococci to produce the gangrenous changes in the dermal structures which resulted in noma.

Why did the experimental noma heal? Is not noma in most instances fatal? Gangrenous stomatitis or noma is not a fatal disease of itself, and the literature contains many reports of spontaneous recovery. It is true that many patients with noma die, but they die from the primary diseases—the leukemia, bronchopneumonia, scarlet fever, typhoid fever, etc.—and not from the noma. It must be remembered that the guinea-pigs were very healthy animals, but in spite of this the phagedenic gangrenous ulcers grew rapidly until sufficient time had elapsed to

permit the development of an active defense mechanism in these animals; then the necrotizing process was arrested and the ulcer healed. If some systemic disease had prevented the guinea-pig from marshaling an adequate resistance against the bacterial gangrene, it is easy to see how the lesions would finally have become very extensive.

The experimental and clinical evidence which has been presented in this case indicates that the noma was an infective gangrene due to bacterial synergism, and that it was not related to the leukemic process.

#### A CASE OF POSTOPERATIVE INFECTIVE GANGRENE OF THE SKIN

Chronic infective gangrene of the skin is occasionally seen following operation for drainage of deep-seated abscesses of the peritoneal and thoracic cavities. Meleney,<sup>1</sup> and later Brewer and Meleney,<sup>13</sup> carefully analyzed such infections and concluded that they were due to bacterial symbiosis, usually that of streptococci and staphylococci. Cullen,<sup>14</sup> Alexander,<sup>15</sup> Gillespie,<sup>16</sup> Shipley,<sup>17</sup> Ballin and Morse,<sup>18</sup> Lynn,<sup>19</sup> Meleney,<sup>1</sup> Baker and Terry,<sup>20</sup> Horsley<sup>21</sup> and others have reported large sloughing gangrenous ulcers of the abdominal wall following the drainage of intra-peritoneal abscesses. Christopher,<sup>22</sup> Ballin and Morse,<sup>18</sup> Poate<sup>23</sup> and

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13. Brewer, G. F., and Meleney, F. L.: Progressive Gangrenous Infection of the Skin and Subcutaneous Tissues Following Operation for Acute Appendicitis: A Study in Symbiosis, *Ann. Surg.* **84**:438, 1926.

14. Cullen, F. S.: A Progressively Enlarging Ulcer of the Abdominal Wall, Involving the Skin and Fat, Following Drainage of Abscesses Apparently of Appendiceal Origin, *Surg., Gynec. & Obst.* **38**:579, 1924.

15. Alexander, E. G.: Postoperative Spreading Superficial Gangrene, *Ann. Surg.* **84**:461, 1926.

16. Gillespie, M. G.: Phagedenic Ulceration of the Skin, *Ann. Surg.* **88**:248, 1928.

17. Shipley, A. M.: Progressive Gangrenous Ulceration of the Abdominal Wall, *Ann. Surg.* **87**:245, 1928.

18. Ballin, M., and Morse, P.: Progressive Postoperative Gangrene of the Skin, *Am. J. Surg.* **11**:81, 1931.

19. Lynn, F. S.: Postoperative Gangrenous Ulcer of the Abdominal Wall, *J. A. M. A.* **97**:1597 (Nov. 28) 1931.

20. Baker, W. H., and Terry, C. C.: A Case of Postoperative Progressive Gangrene of the Skin, *J. A. M. A.* **98**:138 (Jan. 9) 1932.

21. Horsley, J. S.: Certain Symbiotic Bacterial Infections Producing Gangrene with Particular Reference to the Principles of Treatment, *J. A. M. A.* **98**:1425 (April 23) 1932.

22. Christopher, F.: Severe Spreading Carbuncular Infection of the Chest Wall Following Rib Resection under Local Anesthesia: A Case Report, *S. Clin. North America* **4**:795 (June) 1924.

23. Poate, H. R. G.: Spreading Gangrenous Infections, *M. J. Australia* **2**:398, 1930.

Patterson<sup>24</sup> encountered extensive sloughing lesions of the thoracic wall following thoracotomy for empyema.

Fortunately, in connection with Dr. William E. Lower of the Cleveland Clinic, I have had the opportunity to make careful studies of a similar case.

*History.*—A woman, aged 58, was admitted to the Evangelical Lutheran Hospital because of severe hyperthyroidism. After careful preoperative preparation Dr. Lower performed a subtotal thyroidectomy. Following this a consolidation of the lower lobe of the right lung developed. However, she made a rapid convalescence and was discharged on the eighteenth postoperative day.

Four days after returning home, she had a sharp, severe pain in the lower part of the chest on the right side, resulting in a pleural effusion that soon became purulent. She was then admitted to the Cleveland Clinic Foundation Hospital for a rib resection and drainage of the empyema. Pure cultures of nonhemolytic streptococci were recovered from the aspirated pus. She made such an excellent response to the thoracotomy that she was discharged on the eleventh postoperative day in spite of the fact that there was a small amount of purulent drainage from the thoracic cavity. Contrary to expectations the sinus refused to heal, though active treatment was given.

Forty-three days after resection of the rib, she complained of the wound being very painful. On examination, the skin around the ostium of the sinus was found to be hyperemic, swollen, edematous and very tender. She complained of general malaise and had a febrile reaction of 101 F. Next day the inflammatory process had extended 2 cm. beyond the sinus. The peripheral margin of the lesion was fiery red, while the tissue adjacent to the sinus was edematous and swollen and had a peculiar bluish, cyanotic tinge. Peculiarly, there was no evidence of fluctuation, and the drainage from the thoracic sinus had practically ceased. Next day the zone of reaction had extended about 5 cm.; the margins were now dark and necrotic, and the area of ulceration enlarged. Energetic local and systemic therapy was ineffective.

Six days after the onset of this local inflammation, the denuded base of the gangrenous ulcer measured 12 cm. in diameter and involved all of the cutaneous and subcutaneous structures of the right lateral wall of the chest. The base of the ulcer was clean and covered with normal-appearing muscle tissues. The border of the ulcer was formed by gangrenous cutaneous tissue that hung in loose necrotic shreds. Incision into these gangrenous areas did not cause bleeding. The edges of the ulcer were definitely undermined. The zone of reaction formed a rainbow of colors, varying from bluish black on the gangrenous areas to the fiery red in the zone of reaction and then gradually merging into the pinkish hue of normal skin.

Cultures taken from the thoracic sinus proved to be nonhemolytic streptococci, while those obtained from the advancing margin of the ulcer were nonhemolytic streptococci, *Staph. aureus*, diphtheroid bacilli and gram-negative bacilli. Unfortunately, no anaerobic cultures were made.

Realizing the nature of this infection, Dr. Lower excised all of the diseased tissue by means of a high frequency current. Considerable healthy tissue was sacrificed in order to get beyond the zone of the advancing inflammation. Dressings with surgical solution of chlorinated soda and the application of dry and moist heat,

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24. Patterson, H. A.: Progressive Postoperative Cutaneous Gangrene, *Ann. Surg.* 96:1091, 1932.

combined with general systemic measures, resulted in a rapid recovery. The wound healed by cicatrization. It was interesting to note that the thoracic sinus stopped draining just as soon as the ulcer on the wall of the chest was excised.

#### COMMENT

While no attempt was made to reproduce this ulcer experimentally, I feel justified in considering the case one of infective gangrene of the skin caused by bacterial symbiosis. It corresponds in every detail to those so accurately described by Meleney.<sup>1</sup>

The hyperthyroidism, the thyroidectomy, the pneumonia, the empyema and the persistent draining thoracic sinus all helped to reduce the resistance of the patient to a minimum. The purulent discharge from the empyemic cavity, containing the nonhemolytic streptococci, was constantly infecting the cutaneous margins of the sinus tract. Hence the stage was all set for producing an infective gangrenous ulcer. The rapid extension of the ulcer, its destructive nature, its clinical appearance, the isolation of nonhemolytic streptococci and *Staph. aureus* from the peripheral margins of the lesion and its response to radical excision all substantiate the diagnosis of bacterial synergism resulting in cutaneous gangrene.

#### TREATMENT

Procrastination and conservatism have no place in the treatment of infective cutaneous gangrene. Delay increases the gravity of the situation. The rapid extension, the destructive nature and the toxic systemic reaction to the infections demand quick, energetic therapy. It is obvious that the type of treatment employed varies according to the nature of the provocative organisms. The therapeutic measures which are effective in controlling gas gangrene infections are impotent if applied to amebic or fusospirochetal ulcerative necrosis of the skin. Unfortunately, one cannot always wait for the laborious, time-consuming bacteriologic studies to designate the number and type of invading bacteria. In such events, the differentiation between the various forms of cutaneous gangrene depends on the appearance of the local lesion and the systemic response of the patient to those particular infective agents. Meleney has written a most comprehensive and instructive treatise on this subject.

The ideal treatment is early radical excision of the diseased tissue. Conservatism invites recurrences. The line of excision should extend well into the normal tissues, with the hope of thereby removing the advancing inflammatory process as well as the dead and necrotic structures. There is no choice between cautery and knife excision; both are effective. The postoperative therapy involves the use of hot hypertonic magnesium sulphate packs and dry heat and irrigations of the wound with an oxidizing solution. General systemic measures such as

repeated transfusions of blood, the prescription of high caloric diets rich in vitaminic content and intravenous administration of hypertonic solutions of dextrose, arsenicals, vaccines and serums have all proved efficacious in increasing the patient's defensive reactions.

Radical excision of a large gangrenous ulcer is always a mutilating procedure, particularly if it should involve the face, as in the case of noma. Fear of these resulting deformities has invited the employment of temporizing procedures. However, conservative measures fail, and the phagedenic ulceration soon produces hideous deformities that are beyond repair. Early excision minimizes the amount of tissue that must be sacrificed. The majority of deformities can be corrected by plastic surgery. No reconstructive work should be done for several months after the local infection has completely subsided. Usher and Ross<sup>25</sup> have reported the successful plastic repair of a facial defect caused by a destructive nomatous lesion.

Can such cases of postoperative skin gangrene be prevented? In most cases of cutaneous ulceration following suppurative operations, the wounds have been partially closed by suture. Interestingly enough, the cutaneous reaction begins around the suture, often several centimeters away from the infected draining sinus. The constant tension, combined with mechanical irritation of the suture, produces a devitalization of the local tissues, which, taking place in the presence of an infection, may initiate the gangrenous reaction. Prophylactic treatment dictates that all cutaneous wounds should be left unsutured when an intrathoracic or intraperitoneal abscess is being drained.

#### SUMMARY

Two cases of acute infective gangrene of the skin are presented. The first case is that of a Negro boy, aged 3, who had acute myelogenous leukemia complicated by gangrenous ulcerative stomatitis (noma), streptococcic dermatitis and bilateral bronchopneumonia. Experimental studies proved that the noma was caused by a bacterial synergism between the anaerobic micro-aerophilic nonhemolytic streptococci, the fusiform bacilli and the anaerobic *Staph. aureus*.

In the second case a sloughing gangrenous ulcer of the thoracic wall following a thoracotomy for a streptococcic empyema was studied. Bacteriologic, histopathologic and clinical evidence indicates that the cutaneous gangrene was caused by a symbiosis of the nonhemolytic streptococcus and *Staph. aureus*.

Treatment consists of early radical excision of all diseased tissue. Plastic repair of the resulting deformities can be accomplished after the infection has completely subsided.

25. Usher, S. J., and Ross, D. E.: A Case of Cancrum Oris Following Typhoid Fever with Plastic Repair, *Canad. M. A. J.* **25**:446 (Oct.) 1931.

# LATERAL DISLOCATION OF THE WRIST JOINT

REPORT OF A CASE OF RADIOCARPAL DISLOCATION OF THE RADIAL SIDE

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AND

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CHICAGO

The advent of the roentgenogram has added much to the knowledge of injuries of the wrist joint and has perhaps established the fact that dislocations are rare and that apparent dislocations are due to deformities produced by fracture in the region of the wrist joint.

While anterior and posterior dislocation of the wrist is met with, lateral dislocation is apparently rare. In a search of the literature we have not found a case of lateral radiocarpal dislocation. Charles Scudder, in a personal communication, stated that he did not recall having seen such a dislocation and considered it extremely rare. To his knowledge but two cases have been reported, both before the days of roentgen examination. One was recorded by F. H. Hamilton in his book "Fractures and Dislocations," published in 1884; the other was cited in the *Bulletin de la Société de chirurgie de Paris* in 1874. One was the case of a man, aged 47, who fell from a height, sustaining a compound dislocation of the left wrist and a dislocation of the elbow on the same side. F. J. Cotton of Boston informed us that he has never seen a case of lateral dislocation of the wrist. William O'Neill Sherman of Pittsburgh, in a personal communication, reported a single case with late reduction and approximately 50 per cent return of function. He expressed the belief that an immediate reduction would have resulted in a higher percentage of function.

A review of the anatomy of the wrist joint seems necessary to arrive at the mechanism of production of lateral dislocation and the constant and inconstant lesions resulting therefrom. The wrist joint is formed by the distal portions of the radius and ulna, the carpal bones and the proximal portion of the metacarpal bone. The radiocarpal joint, or wrist joint proper, is formed by the articulation of the radius with the proximal rows of the carpal, scaphoid, semilunar and cuneiform bones. The surface is concave in the anterior, posterior and lateral directions for the reception of the carpus, which contributes largely to the flexibility and stability of the wrist joint. It must be noted, however, that when the hand is held in the axis of the forearm the radius is chiefly in contact with the scaphoid and a part of the semilunar bone. The portion in contact with the semilunar bone is the inner portion or *discus articularis*.

When the hand is adducted or in a position of ulnar flexion the ulnar portion of the radius comes into complete articulation with the cuneiform bone and forms to some degree a fulcrum.

The intracarpal joint is formed by articulation of the first and second row of carpal bones. The arrangement of the joint does not permit lateral movement. The ligamentous structure of these joints consists of a capsular ligament common to all and extending from the articular borders of the radius and ulna to the base of the metacarpal bones. Between these attachments it connects with the first and second rows of carpal bones. It is reenforced by accessory bands, the lateral ligament being the most common. The external lateral ligament extends from the radial styloid to the base of the first metacarpal bone and is attached to the tubercle of the scaphoid and trapezium. The internal lateral ligament extends from the ulnar styloid to connect with the fifth

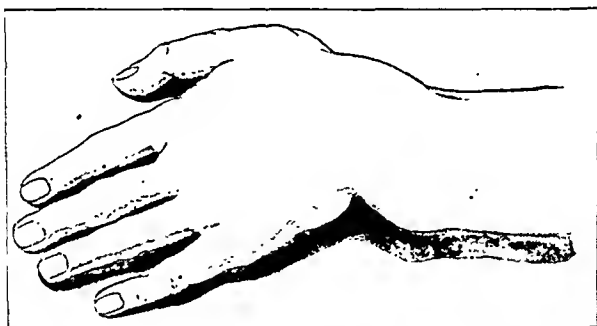


Fig. 1.—A drawing made at time of the first examination showing the marked deformity of the wrist joint. The hand is slightly pronated in the ulnar flexion position.

metacarpal, cuneiform and unciform bones. On the strength of these ligaments the stability of the wrist joint depends. Interosseous ligaments formed by extension of the general capsular ligament unite the individual bones. The motions of the carpal or wrist joint are flexion, extension, adduction and abduction, the major portion occurring at the radiocarpal joint.

#### REPORT OF CASE

On Sept. 10, 1930, J. H., a man aged 28, was admitted to the Woodlawn Hospital in a mild degree of shock as the result of an automobile accident. After the shock had been combated the following history was obtained:

While he was driving a truck under a viaduct the left front wheel hit a rather deep hole, throwing the steering wheel suddenly to the left. The wheel came up out of the hole, and hit the abutment, and the truck stopped. The patient's hands were holding the horizontal cross-bar of the steering wheel when the accident occurred.



On examination the hand was found to be swollen. There was a marked deformity at the wrist joint, part of which was due to swelling and edema of the tissues. The hand was held in a slightly pronated and ulnar flexion position. Figure 1 is a drawing made by Dr. Grimm at the time of the examination. Our impression was that there was probably a fracture of both bones of the lower part of the arm, although the carpal bone seemed to be dislocated from the radial side. There was paralysis with loss of sensation of all the fingers of the left hand except of the little finger.

The roentgen examination was made by Dr. Harry Olin and was as follows: Roentgenograms of the wrist and lower two thirds of the forearm revealed a lateral dislocation of the wrist joint toward the radial side with fracture of the scaphoid, its ulnar one half being displaced, and displacement of the cuneiform bone, both of which approximate the articular surface of the radius. In other



Fig. 2.—Lateral and anteroposterior roentgenograms taken before reduction.

words, the wrist was displaced laterally, carrying with it the ulnar half of the scaphoid and the cuneiform bone. In this position the styloid of the radius overlay the os magnum and the trapezium overlay the trapezoid. The hand was in the position of extreme adduction in the pronated position. There were several small, loose fragments of bone on the internal surface of the cuneiform bone, probably due to injury of the cortex in this region. The lateral view showed no displacement of the wrist joint either anteriorly or posteriorly. The soft tissues about the wrist were moderately thickened. Figure 2 shows the dislocation before reduction.

Under fluoroscopic guidance with manipulation, with the patient under ethylene anesthesia, the lateral dislocation was reduced by firm traction, while the hand was pulled under extension to ulnar flexion. As noted in the roentgen report, the scaphoid bone was fractured. The hand was dressed with a light anterior splint with very little pressure on the arm. Figure 3 shows the dislocation after

reduction. The scaphoid and semilunar bones were in position with slight displacement downward of the radial half of the scaphoid. The trapezium was displaced toward the ulnar side and still overlay the trapezoid, comparison being made with the right, or uninjured, wrist.

In summary, the case was one of lateral, radial displacement of the left wrist with fracture of the scaphoid and displacement of the trapezium. Reduction was accomplished in good position, but the displacement of the trapezium persisted.

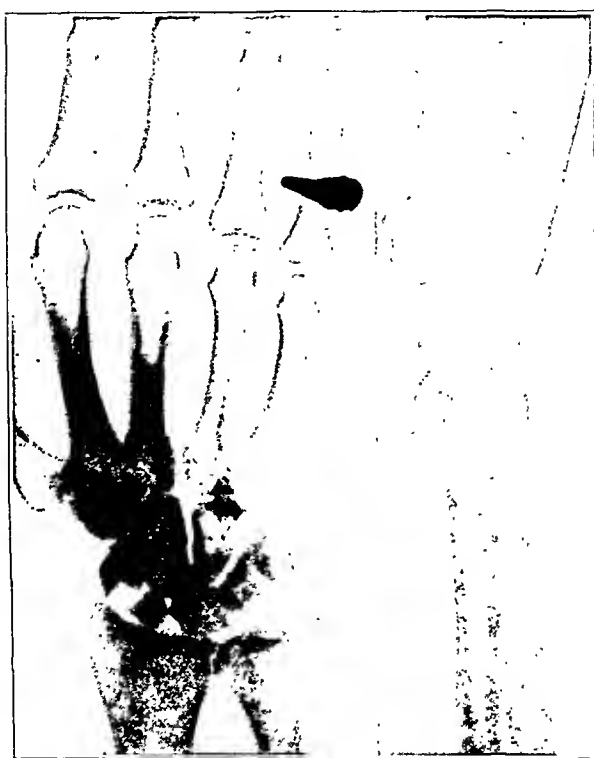


Fig. 3.—Lateral and anteroposterior roentgenograms taken after reduction.

The mechanism of this dislocation is a problem. It seems clear that when the front wheel struck the hole marked adduction or ulnar flexion of the wrist was produced, and that while in this position the sudden impact of the forearm on the fixed hand with the discus articularis in contact with the cuneiform bone forced the carpal bones to a radial dislocation. The conclusions are that carpal dislocation to the radial side is produced when the hand is in extreme ulnar flexion and, likewise, that carpal dislocation to the ulnar side can be produced only when the hand is in extreme abduction. It seems evident that in

this case the capsular ligament and both the external and the lateral ligament were ruptured in the production of the dislocation.

Dr. Sherman, in speaking of the mechanism of this dislocation, said: "One can only believe that the hand was fixed on the cross-bar of the steering wheel and acted as a fixed joint, and at the moment of impact the force of the body was transferred through the arm on the diagonal, causing the external dislocation of the forearm."

When asked his opinion of the mechanism after viewing the roentgenograms, Dr. Cotton said: "I should think that it was almost impossible for it to happen after a full lateral thrust. It must have come out through a torsion strain, and my guess would be flexion and pronation, but this is purely a guess."

The roentgenograms were submitted to Dr. Scudder also. Concerning the mechanism of production he said: "I do not think one can formulate the exact forces at work in this case. The bizarre type of fracture and dislocation make one quite dizzy and certainly demand very special skilled observation and treatment."

The patient was seen several months after reduction was made. The function of the wrist was fairly good. He passed out of our hands a few days after reduction was made into the hands of an insurance company, because of the compensation law.

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PRIMARY THROMBOSIS OF THE AXILLARY VEIN  
AN ANATOMIC AND ROENTGENOLOGIC STUDY OF CERTAIN ETIOLOGIC  
FACTORS AND A CONSIDERATION OF VENOGRAPHY AS A  
DIAGNOSTIC MEASURE

J. ROSS VEAL, M.D.

AND

ELIZABETH M. McFETRIDGE, M.A.

NEW ORLEANS

Matas'<sup>1</sup> comprehensive study of primary thrombosis of the axillary vein makes it unnecessary for later writers to dwell at any length on the general aspects of the condition and goes far to answer his own criticism that the American literature is singularly barren of contributions to the subject. He is undoubtedly correct in his contention that even a casual survey of recent English and continental publications would increase to one hundred or perhaps more the number of cases (seventy-four) collected by Bruno Paggi in 1933. Nevertheless, the disease is unusual enough to warrant our recording two additional cases, neither of which belongs to the so-called "effort" group. We desire to report also certain studies which we have made on the living subject and on fresh autopsy material in an effort to unravel the still dubious etiology and which are not in accord with the theories heretofore advanced to explain it.

REPORT OF CASES

CASE 1.<sup>2</sup>—A youth, aged 19, who was in the habit of sleeping with his right arm above his head, was suddenly wakened from sleep twenty-four hours before admission by a pain which extended from the axilla down the whole arm and was associated with a stinging sensation in the finger tips. The arm had begun to swell almost simultaneously with the onset of the pain. The previous history was without importance, and the only relevant data, aside from a secondary anemia presumably due to intestinal parasites, concerned the intense swelling of the right arm and hand. The edema was of the brawny, pitting type, and the whole affected extremity was slightly colder than the left arm. The painful cord usually palpable in the axilla in acute cases of thrombosis of the axillary vein was not felt during the entire period the patient was under observation.

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From the Department of Surgery of the Louisiana State University School of Medicine.

1. Matas, R.: On the So-Called Primary Thrombosis of the Axillary Vein Caused by Strain: Report of a Case with Comments on Diagnosis, Pathogeny and Treatment of This Lesion in Its Medico-Legal Relations, *Am. J. Surg.* **24**: 642, 1934. This article contains an extensive bibliography.

2. This case is reported through the courtesy of Dr. E. J. Richard.

A venogram made with a stabilized solution of thorium dioxide on the third day after admission showed a point of obstruction in the axillary vein distal to the first rib, with a backflow of the opaque medium into the brachial vein and as the result of the intense swelling of the extremity, a marked narrowing of all the veins visualized.

Treatment since admission had consisted of elevation of the arm on pillows and the use of a heat tent. In order to make an injection into the basilic vein it was necessary, because of the intense edema, to make a small incision over the vein. Through this incision edematous fluid promptly poured out and continued to flow profusely for seven days, at the end of which the arm was practically normal in size and appearance. The patient was discharged three days later, with instructions to return at the first evidence of any recurrence of the trouble and if no recurrence took place to report in three months. He has not been heard from since his discharge two months ago, and it is assumed that he has remained well.

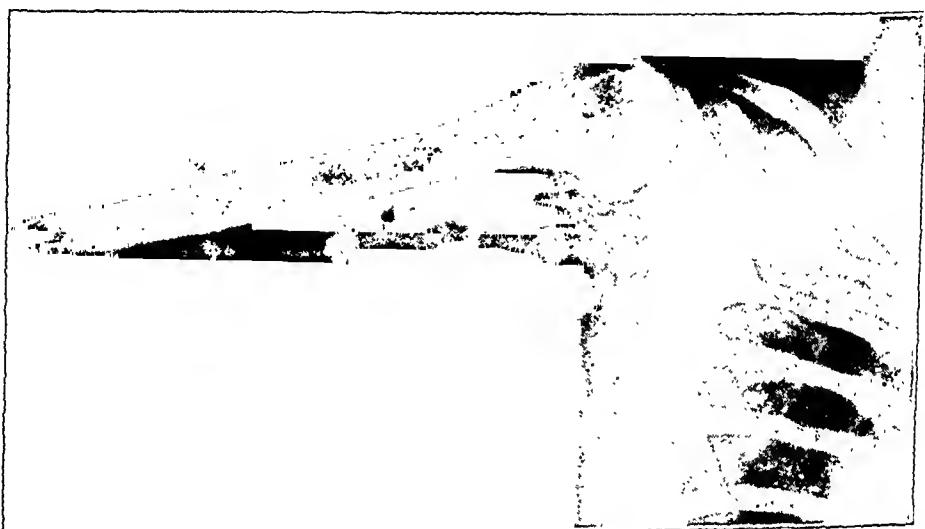


Fig. 1 (case 2).—Roentgenogram showing occlusion of the right axillary vein, with formation of new collateral vessels, in a patient who had primary thrombosis of the axillary vein seven years before.

CASE 2.—A woman, aged 22, exhibited large, dilated veins on the right shoulder and upper right portion of the chest, which rendered her conspicuous when she wore evening dresses. Careful questioning elicited no information beyond a history that an acute swelling of unknown origin had appeared seven years before. It had involved the whole right arm and hand and had been accompanied by pain in the axilla and arm, but it had subsided in a few weeks without active treatment. The aforementioned condition in the veins had developed gradually since that time, but there had been no further symptoms other than a slight enlargement of the arm, never more than transitory, after any unusual exertion.

Physical examination gave essentially negative results except for the slight enlargement of the right arm and the presence of large, dilated veins which coursed over the anterior portion of the right shoulder and spread out over the upper part of the chest and the breast. Venography (fig. 1) showed an obstruction in the axillary vein distal to the first rib, as in case 1, and a rather extensive collateral circulation. No treatment was indicated.

## COMMENT

The history in case 1 is typical of that in the few cases reported, chiefly from the foreign literature, in which the thrombosis of the axillary vein develops in the absence of trauma. The more usual variety follows severe effort, and Gould and Patey,<sup>3</sup> who have reported the largest single series on record (eight cases) have outlined a composite picture of the condition from their own experience: A young man, a few hours after some unusual exercise with the right arm elevated, has pain or swelling or both, increasing in the course of the next day or two until the entire arm is swollen and somewhat cyanotic. There are no constitutional symptoms, and usually no elevation of temperature is observed. The whole arm is the seat of a solid swelling, dilated superficial veins running from the upper part of the arm to the pectoral region, and in the axilla is a firm cord, sometimes traceable to the elbow, which corresponds in position to the axillary vein. With rest and elevation of the arm the swelling slowly subsides; power of motion of the joints, which was at first limited, begins to return, and at the end of a few months normal function is fully restored except that there may be some pain when the arm is fully elevated and some permanent, usually slight, dilatation of the superficial veins on the shoulder.

The immediate cause of the accident varies widely. In the majority of reported cases there is a history of unusual effort. Schepelmann's patient sustained his injury in trying to control a wild horse; Lahaussais' and Van der Hoeven's patients fell from horses, and Austin's patient also sustained a fall. Baum's patient, a woman, had been moving heavy furniture, and Rosenthal's, another woman, had been beating clothes. Winterstein's patient, a weaver, had been piling heavy bolts of cloth on a shelf, using his left arm—it will be noted that whenever the left arm is involved the patient is left-handed or has used the left arm in some unusual manner. Schwindt's<sup>4</sup> patient had been pulling tents from trees, in the process of fumigating citrus trees, which involves extreme muscular effort with the arms above the head. Horton's<sup>5</sup> patient had dug a hole for a post with a heavy steel crowbar. The subject of Matas' detailed report sustained his injury when the wrench he was using slipped and he was thrown forward on his arm.

All these patients, it will be noted, had been engaged in some unusual, violent effort when their injuries occurred, but against their cases must be set those which followed such simple acts—"banal," as Matas calls them—as cracking a whip or even stirring a Christmas pudding. In one

3. Gould, E. P., and Patey, D. H.: Primary Thrombosis of the Axillary Vein; Study of Eight Cases, *Brit. J. Surg.* **16**:208, 1928.

4. Schwindt, J. K.: Traumatic Thrombosis of the Upper Extremities, *California & West. Med.* **27**:635, 1927.

5. Horton, B. T.: Primary Thrombosis of the Axillary Vein, *J. A. M. A.* **96**:2194 (June 27) 1931.

of the eight cases reported by Gould and Patey the exciting cause was not determined, but in the others the immediate causes included the playing of a game of golf, the use of an electric cutting machine, hammering, hanging curtains, lifting jars to a shelf and cleaning ceilings. The effort, in no case, seems particularly strenuous, but in nearly every case, the authors pointed out, the effort was one to which the patient was not accustomed.

The case reported by Firth and Mackay, that of a girl who stirred a pudding, is quite unusual in that a month or two after the condition had subsided in the right arm it occurred in the left arm. Equally unusual is the case reported by McGoogan and Simmons,<sup>6</sup> in which the thrombosis developed on the fourteenth day of an almost afebrile con-



Fig. 2 (case 2).—Venous collaterals (infra-red photography) of the axillary region shown by roentgenogram in figure 1.

valescence from a cesarean section performed on a patient with nephritic toxemia. The cases in which no effort of any sort was apparent, the condition coming on during sleep, we have already commented on.

#### DIAGNOSIS

The clinical diagnosis rarely offers any difficulties. The characteristic features are the suddenness of onset and the rapid development of the swelling, which occurs almost simultaneously with the onset of the pain. A history of antecedent, indirect trauma can be elicited in most cases, and in most acute cases the affected vein can be palpated in the axilla as a firm, painful cord. In advanced cases the "venous ecstasies" (fig. 2), as Matas termed the collateral venous tributaries,

6. McGoogan, L. S., and Simmons, E. E.: "Effort" Thrombosis of Subclavian Vein in Puerperium, *Nebraska M. J.* 18:289, 1933.

are also characteristic. The studies on the blood which have been made in a few cases do not show characteristic changes aside from that demonstrated by Horton, namely, that the oxygen content of the venous blood on the affected side is considerably less (43 volumes per cent) than on the unobstructed side (70 volumes per cent).

The differential diagnosis includes tumors, enlarged lymph nodes, fractures, arteriovenous and other aneurysms, substernal goiter, cervical ribs and other bony anomalies, regional extensions of infections, axillary phlebitis as the complication of other diseases, occasional central and peripheral neuropathic disorders, the scalenus anticus syndrome and cardiac failure. The majority of these conditions carry their own diagnosis, and confusion is unlikely. In most cases the onset is too sudden to permit the possibility that diseases of long standing, such as most of those just named, could be responsible. Roentgen examination, which has long been used to eliminate the diagnosis of such causative conditions as bony abnormalities and tumors of various kinds, should in the future, if used by the technique of vasography which will be described later in this paper, establish the diagnosis absolutely in any doubtful case, since it will determine beyond doubt the point and type of obstruction.

It is interesting that Gould and Patey reported one case, so far as we know the only one reported in connection with this condition, in which another disease was mistaken for primary thrombosis of the axillary vein. The patient presented an apparently perfectly typical picture of the condition except that it occurred on the left side, a fact which, in a right-handed subject and without any reasonable cause for the location of the trouble, should perhaps have given rise to suspicion. The edema promptly disappeared under conservative treatment, and its true origin, an aneurysm of the arch of the aorta, was not discovered until eight months later.

#### TREATMENT

While treatment is not our chief concern, we shall mention it briefly, partly because, in case 1 of this series, we unwittingly employed a method which improved the condition and partly because we desire to point out that vasography is also useful in setting the indications for operation.

Conservative measures, which should always be employed first, include rest, immobilization or elevation of the arm, bandaging, which gave particularly good results in Horton's case, and physical therapy. Under such treatment in ordinary cases edema is relieved, and recanalization of the vein takes place or an adequate collateral circulation develops. Matas and other authors have taken the position that when



results do not promptly appear under this system of therapy operation should be resorted to. The procedure should be either simple excision of the clot, which is ordinarily sufficient, or excision of the whole affected segment. Vascular surgery of this type is, of course, not free from risk.

Worth noting also is the case reported by Moure and Martin and quoted by Matas, in which exploration revealed an ecchymosis of the inner border of the coracobrachialis muscle. The original trouble was obviously a hematoma, which had later been absorbed, leaving a considerable collection of (sterile) serum in the intramuscular spaces. Cure was complete within three weeks after operation, and the whole case seems to bear out the suggestion of Löhr and others as to the propriety of exploration in certain cases to eliminate the possibility of extravenous pathologic changes.

In one of Wilson's<sup>7</sup> cases multiple incisions, about thirty in all, were made to relieve the intense edema, and this author expressed the belief that the discharge of serum by these routes initiated the improvement. Gould and Patey contended that such drastic measures are unnecessary, but it is interesting to recall that in one of our own cases, in which the thrombosis was observed in the acute stage, the same treatment was unwittingly administered, as we have already noted, and prompt improvement followed the profuse discharge of serum through the incision made for the purpose of introducing the opaque medium.

Venography, in our opinion, can be utilized for determining the indications for operation: It settles absolutely, as we have already pointed out, the question of whether obstruction exists and whether the condition is of intravenous and extravenous origin, and in most cases the answer also settles the question of whether surgical intervention would be helpful or useless.

#### PROGNOSIS

We cannot agree with authors who state that the prognosis is uniformly good. For life it undoubtedly is. In none of the reported cases did the patient die of the accident—although one or two died of other diseases associated with it—except in the case reported by Moure and mentioned by Matas with the comment that the patient's condition does not properly belong in the classification under consideration. In that case all the facts were opposed to a diagnosis of primary thrombosis of the axillary vein: The patient, a 70 year old woman, died, four days after sustaining a fracture of the neck of the humerus, from an embolus which was proved at autopsy to have originated in the subclavian vein on the same side as that on which the fracture occurred. In only one

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7. Wilson, G.: Brachial Monoplegia Due to Thrombosis of the Subclavian Vein, *Am. J. M. Sc.* **163**:899, 1922.

authentic case did embolism occur, and in that instance Schepelmann explored the affected area and removed the clot.

In many cases prompt improvement follows conservative treatment, or even occurs without treatment, and there is no recurrence. In other cases, as in case 2 of this series mild residual symptoms are noted over many years. In still other cases there is a recurrence whenever the person endeavors to resume his former occupations, and the accident assumes, as Matas points out, a medicolegal aspect. This happened in the case which forms the basis of his own extensive study, and in the case reported by Jeameney and Mathey-Cornat recurrences persisted for six years, or until the whole affected segment was excised.

#### THEORIES OF ETIOLOGY

Before passing on to our own investigations as to the origin of primary thrombosis of the axillary vein it is necessary to mention briefly the theories formerly or presently held, many of which predispose one to agree with Shoemaker, who said in discussing Schwindt's case, that the whole state of thrombosis is so inexplicable that it should perhaps be regarded simply as an act of God. The suddenness of onset, as we have already intimated, seems to indicate that none of the aforementioned predisposing causes is an important factor, for the factors which precipitate the attack are entirely inconstant. Wilson attributed his first case to tuberculosis and the second to syphilis, but the mere reading of his report establishes the fact that both these factors were coincident rather than causative. Lowenstein<sup>8</sup> was probably right in saying that syphilis as a cause was invoked in that case and in others merely for the reason that it is invoked in any poorly understood case. Ruge's contention that the thrombosis might be the first sign of a latent cardiac condition may be promptly dismissed, for there is nothing in the clinical course of any reported case to support such a theory. The acts and positions which precipitate thrombosis of the axillary vein are done so often and assumed so frequently by so many persons, in so much more exaggerated a fashion than that which precipitates the attack, that if they alone were responsible the disease would be frequent rather than, as it is, infrequent. In certain cases, as in that of the patient operated on by Moure and Martin, quoted by Matas, an extravascular cause seems to be operative, perhaps the rupture of muscle fibers with consequent obstruction of the vein by external pressure produced by a hematoma or by an accumulation of serum, if not by both. McGoogan and Simmons suggested a similar origin for the condition in their own

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8. Lowenstein, P. S.: Thrombosis of the Axillary Vein, an Anatomic Study, *J. A. M. A.* 82:854 (March 15) 1924. This article contains an extensive bibliography.

case; their idea was that the thrombosis was produced by the patient's pulling herself up in bed during her convalescence. But again, if such a factor were a constant cause, a large number of convalescent persons would unquestionably exhibit the disease.

The infectious theory, as Matas pointed out, naturally arises in any thrombotic condition, but both clinical and bacteriologic evidence oppose it. Of twenty-seven cases in which operation was performed, data as to bacteriologic findings are available in only seven; the findings were positive in three, it is true, but in each of these cases there was definite evidence of a septic phlebitis in the vessel wall, a finding which is not in accord with the clinical history and termination in the great majority of cases. In Matas' opinion the "infectious traumatic phlebitis" theory of the French school is an unwarranted and untenable assumption.

Matas showed an inclination to give much more weight, however, to the sympathetic theory recently advanced by Cottalorda, on the basis of operation in his own case, which revealed not a thrombus but a rigid spasm of the vessel wall. The theory, to state it briefly, is that the vascular lesion originates in a venous spasm induced by sympathetic irritation, which in turn is the result of trauma. The thrombus is a possible but not an essential part of the picture. This view, Matas stated, is quite in accord with the theories of Leriche, who expressed the belief that venospasm is the effect of the vasomotor reflexes which originate in the perivenous sympathetic nerve fibers.

The close relationship between the vascular system of the axilla and the nerve distribution in this area makes it not unreasonable, as was pointed out by Wexberg, of the department of psychiatry of the Louisiana State University School of Medicine, in a recent discussion of this condition, that some neurologic factor may later be found to be of considerable importance. It will be remembered that the axillary vein lies on the medial side of the axillary artery, partially overlapping it, and that between the two vessels lie the medial cords of the brachial plexus, from which spring the median ulnar and medial anterior thoracic nerves. In Wilson's case, in which a paralysis of the arm was associated with the thrombosis of the axillary vein, the paralysis was undoubtedly due to the pressure of the obstructed vein on the brachial plexus.

Von Schrötter, who reported the first case in 1884, although the condition had unquestionably been described by Sir James Paget nine years earlier, expressed the belief that the thrombosis originates in a sudden stretching and compression of the vein after an effort, which produces a localized phlebitis with consequent damage of the vessel wall. Cadenat, who collected data on twenty-seven cases in 1920, considered the cause to be a venous dilatation and stasis due to expiratory effort, combined

with injury to the endothelium of the venous tributaries at their junction with the axillary vein as the result of a single or of repeated muscular strain. Willan suggested that the condition results from trauma to the head of the humerus, and also advanced the idea, which has been more or less widely held ever since, that the axillary vein suffers damage from the outer border of the first rib during vigorous exercise with the arm in the abducted position.

Schwindt, in an extensive study of thrombosis, quoted Welch to the effect that the factors which govern the slowing of the blood stream in the veins, supposedly the underlying factor in all thrombotic states, include "flow from the smaller into larger channels, presence of valves, and fixation of the venous wall in certain situations to fascia and bones," all of which factors are embraced in a striking combination in the venous supply of the shoulder girdle. Schwindt pointed out that the axillary subclavian vein is large and has several valves and several small tributaries and that there is a fibrous attachment to the costocoracoid ligament, to the clavicle above and sometimes to the rib below. He then referred to the arguments of Rosenthal and Pellows: When the arm is elevated, intrathoracic pressure or expiration is directed outward, through the subclavian vein, and unusual muscular contractions about the veins in the arm direct the peripheral force inward through the axillary vein, the meeting of these opposing forces under the clavicle producing a slowing of the stream at the precise point where the vein presents all the anatomic peculiarities which Welch considered competent to induce thrombosis.

Piccagli,<sup>9</sup> the latest writer on the subject, expressed the belief that the anatomic relations of the axillary vein and its tributaries in the region of the costocoracoid membrane are the chief factors and that in his own case the forceful muscular contraction may have torn the wall of the vein, with resulting injury to the intima. Taylor,<sup>9a</sup> in reporting two cases of thrombosis of the subclavian vein, with probable involvement of the impalpable portion of the axillary vein, both in patients who engaged in rowing, pointed out that in neither of these cases could the position of abduction have played any part, since that position is not assumed in rowing. Taylor placed the responsibility in these two cases on the final maneuver in the stroke, which introduces the position of adduction, but it should be noted that that factor does not enter into any other reported case. In support of his theory he mentioned that Appleton, of the Cambridge School of Anatomy, demon-

9. Piccagli, G.: Traumatic Thrombosis of the Right Axillary Vein, *Chir. d. org. di movimento* **19**:186, 1934.

9a. Taylor, C. H. S.: Primary Thrombosis of Subclavian Vein, *Brit. M. J.* **2**:818 (Nov. 4) 1933.

strated to him that by a certain downward motion of the shoulder, with the arm hanging, which simulates the final motion of rowing, the subclavian or axillary artery, and presumably the corresponding vein also, could be so compressed as to stop the radial pulse. Since the axillary vein ends at the outer border of the first rib, Taylor added, it is not subjected to bony pressure as is the subclavian vein, and he thought it possible, that thrombosis of the axillary vein actually originates in the subclavian vein.

However much they may differ as to the how and wherefore of the mechanism, all recent students of thrombosis of the axillary vein agree that trauma, plus some anatomic predisposing cause, is the responsible factor. Lowenstein, who was the first to attack the subject from any but a theoretical point of view, made dissections of the axillae of thirty cadavers and studied transverse and sagittal sections of six additional bodies. As the result of this study he advanced the following theory: The axillary vein is distended by the abduction or extension and lateral rotation of the arm. Venous stasis or circulatory slowing is brought about by the forced expiration that accompanies effort. Under these circumstances pressure on the vein by the costocoracoid ligament, furthered by the subclavius muscle, is sufficient to bring about changes in the vascular endothelium which are, in turn, sufficient to cause thrombosis of the axillary vein.

Gould and Patey, continuing Lowenstein's work, injected plaster of paris into the axillary veins of cadavers with the arm in the abducted position. In two instances they observed broad, deep grooves from the pressure of the subclavius muscle, and in another, a shallow groove corresponding to the position of the costocoracoid ligament. In still other dissections they noted that a practically constant anatomic feature of the vein at the level of the subclavius muscle was the presence of a competent bicuspid valve which was so placed that the pressure of the muscle stretched the wall of the vein in the long axis of the valve. The valve cusp, regardless of location, is always a delicate structure, composed only of a thin sheet of fibrous tissue covered on either side with endothelium. Gould and Patey's theory is that the pressure of the subclavius muscle is responsible for trauma to the vein and that rupture of the delicate subclavio-axillary valve is the fundamental pathologic lesion, while the position of abduction and the expiratory effort resulting in distention of the vein are predisposing factors.

None of these theories, it will be noted, explains why, if a common anatomic factor is responsible, the condition does not occur more often, and some of them do not stand up in the face of the evidence. Gould and Patey's theory, for instance, that the primary lesion is in the subclavio-axillary valve, is overthrown by the fact that in the cases in

which surgical intervention has been practiced, the position of the thrombus is not constant. The one thing that would settle the dispute, a careful autopsy on an affected subject, is lacking, and Wilson was quite right in regretting that in his first case, in which necropsy was performed, entire attention was concentrated on the obvious thoracic condition, tuberculosis, and the affected vein was not dissected. It seemed to us questionable that dissections on prepared cadavers, however carefully they may be made, are exactly comparable to such dissections on fresh material, and we decided to undertake an investigation with such material and to combine it with a study in the living subject by means of

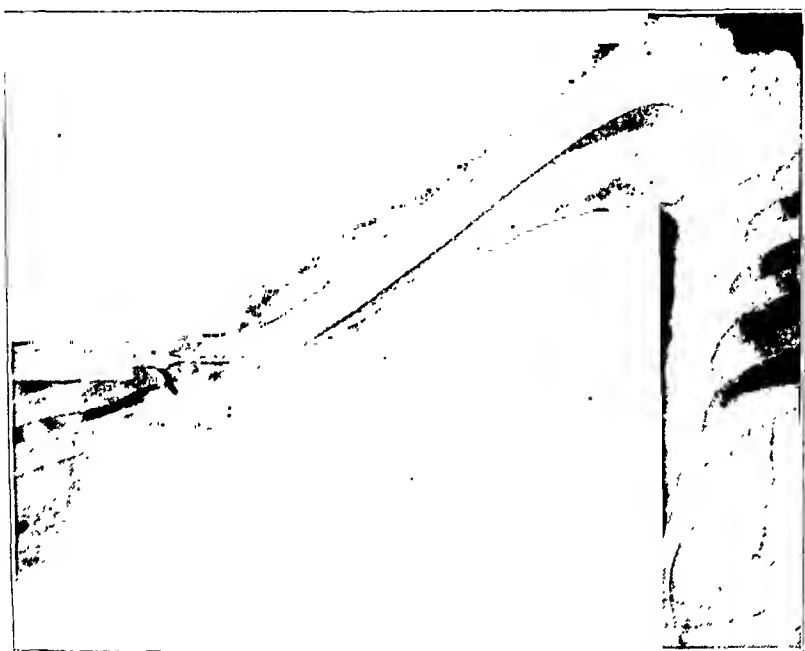


Fig. 3.—Roentgenogram of normal basilic and axillary veins, showing valves of the veins.

venography with thorotrast<sup>10</sup> (stabilized thorium dioxide solution), the use of which in the two cases which had come under our observation had been helpful.

#### NEW DATA

Stabilized thorium dioxide solution (thorotrast Heyden) is an opaque medium of practically the same viscosity as blood and miscible with it,

10. Thorotrast is not acceptable to the Council on Pharmacy and Chemistry of the American Medical Association. A preliminary report appeared in the Journal of the American Medical Association of Dec. 24, 1932, p. 2183.

but of a higher specific gravity. Its toxicity is negligible, and we have used it for the last two years, without ill effects of any sort, in a study of peripheral vascular disease. There seemed to be no reason, therefore, for not using it in the first case of thrombosis of the axillary vein which we observed, and for not continuing its use thereafter. At first thought, it might seem somewhat unsafe to inject a foreign substance into the vein in a case of suspected thrombosis, but the amount

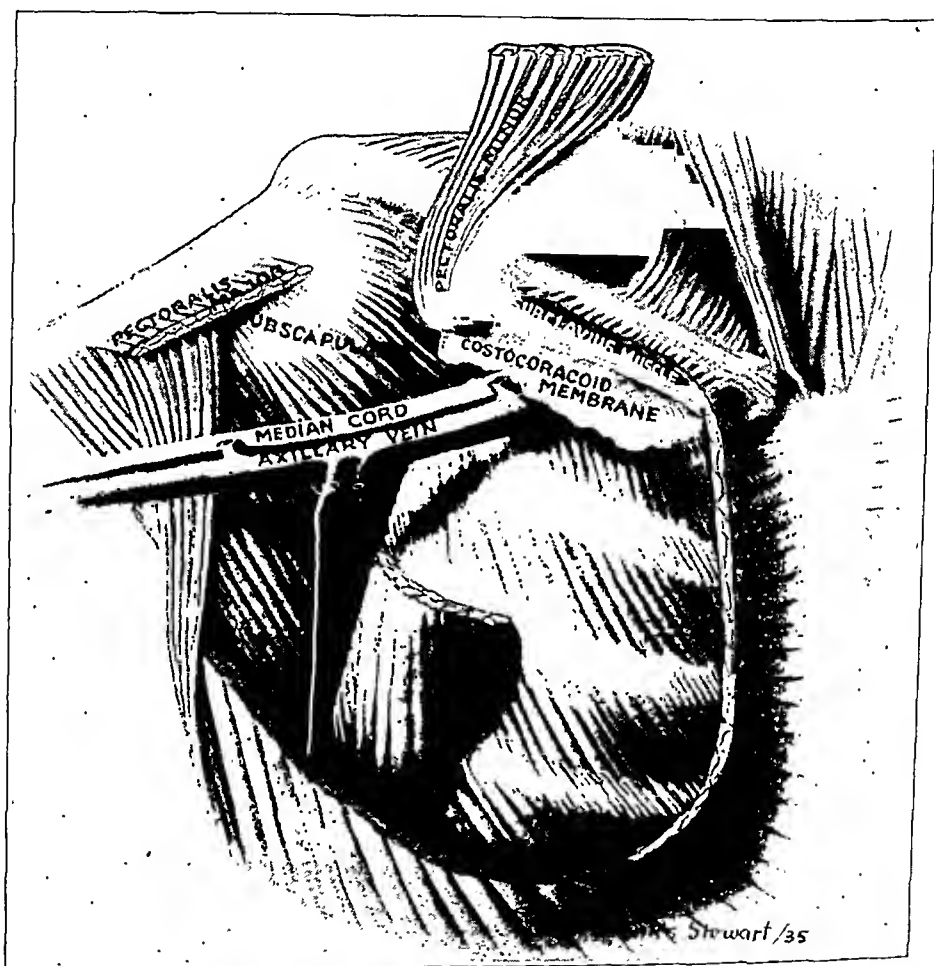


Fig. 4.—Drawing illustrating anatomic relations of parts of the axillary region when the arm is held at an angle of 45 degrees to body.

used is so small, never exceeding 5 cc., and the injection is given with so little pressure that the risk of disturbing the thrombus is academic rather than real. In the normal subject, on whom all our later studies were made, injection of 5 cc. of thorotrast into the basilic vein outlines that vein and the axillary and subclavian veins and, occasionally, the upper part of the superior vena cava and some of the venous tributaries as well (fig. 3).

Before proceeding to a discussion of our findings in these cases, it is necessary to recall certain points of anatomy (fig. 4). The axillary vein is a continuation of the basilic vein and extends as such from the lower part of the teres major muscle to the outer border of the first rib, at which point it becomes the subclavian vein. Thence it continues to the sternal end of the clavicle, where it unites with the internal jugular vein to form the innominate vein. Its tributaries include the brachial vein, which flows into it near the lower border of the subscapularis muscle, the cephalic vein, which flows into it near its termination, and other tributaries corresponding to the branches of the axillary artery and including the thoracic, thoraco-acromial, lateral thoracic, posterior subscapular and posterior and anterior circumflex veins.

The axillary vein passes over the subscapularis muscle, which is attached to the head of the humerus at the lesser trochanter, and under the pectoralis minor muscle. As it passes over the first rib to become the subclavian vein it is covered by the costocoracoid membrane and ligament and the subclavius muscle. Its relation to the regional nerves has already been mentioned.

The anatomic points which we have just outlined can be clearly demonstrated in a normal subject by injecting thorotrast into the basilic vein by the technic already described (fig. 3), the exposure being made on a 14 by 17 inch (35.56 by 43.18 cm.) plate just as the last cubic centimeter of the solution is injected. The anatomic relationship immediately changes, however, when the factor of movement is introduced, as we were able to prove by further roentgen studies with this medium. The vein, being only loosely attached to the surrounding structures, can accommodate itself to moderate changes in position without undergoing material alteration in size. On the other hand, when the arm is hyperabducted and externally rotated the relations between the vein and the subscapularis and the relations between the vein and the head of the humerus are immediately altered (fig. 5).

In the position of hyperabduction and external rotation, as the subscapularis muscle comes to lie between the vein and the head of the humerus, there is a compression of the vein as it passes over it that is entirely absent in the position of internal rotation. Again, when the arm hangs by the side the vein is widely separated from the head of the humerus, but as the position of abduction and external rotation is assumed, it approaches closer and closer to it. The scapula and clavicle are elevated; the muscles attached to the shoulder girdle are put on a stretch, and the axilla becomes a flattened instead of a pyramidal surface.



As a result of these changes the axillary vein is also elevated and held in the new position, in close approximation to the subscapularis muscle near its insertion into the lesser trochanter of the head of the humerus, the compression already described occurring as the complete position of abduction and external rotation is assumed.

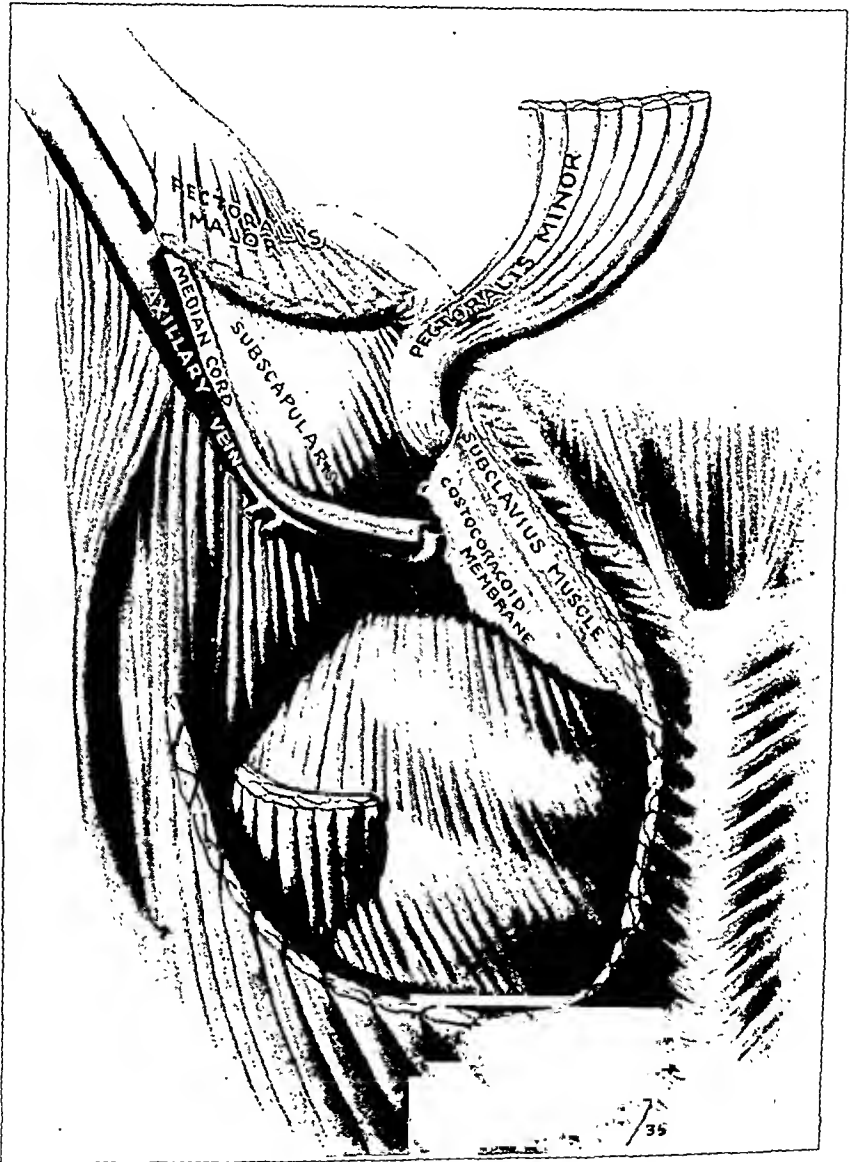


Fig. 5.—Drawing illustrating anatomic relations of parts of the axillary region when the arm is in a position of hyperabduction and external rotation. Note the constriction of the axillary vein against the subscapularis muscle and the stretching of the vein just proximal to the point of constriction.

By roentgen evidence (fig. 6) the obstruction hitherto assumed to occur over the first rib is actually not at that site but rather at the point at which the vein passes over the subscapularis muscle in the position of

hyperabduction and external rotation, and this fact we also established by the dissection of fresh autopsy material. It is true that as the vein crosses the first rib it is more oval than it normally is, and slightly flattened, but a true constriction is not present, nor could we detect any material alteration in the actual venous diameter. We assume, therefore, that Lowenstein's and Gould and Patey's observations, which are contradicted by our own findings, differ from them because they were made on fixed instead of on fresh material.



Fig. 6.—Roentgenogram showing point of constriction of the axillary vein below the head of the humerus against the subscapularis muscle in a position of hyperabduction and external rotation.

The stretching of the vein, which several theories assume as the responsible factor in thrombosis of the axillary vein, was also studied in fresh autopsy material. The vein was exposed without disturbing the subclavius muscle, and care was taken to preserve as much as possible of the costocoracoid membrane and the costocoracoid ligament. Then, with the arm raised at an angle of 45 degrees to the body, the course of the

vein was outlined by means of small pins placed at equal distance from each other, and its length was measured, this measurement being compared with a similar measurement taken later under the same circumstances, but with the arm externally rotated and hyperabducted. The only part of the vein found to have stretched was the portion just proximal to the head of the humerus and just proximal also to the point at which in our roentgen studies constriction had been observed. In the subject under observation the variation in the length of the vein in the two positions was 0.8 cm.

We then proceeded to study the effect on the rate of the blood flow and the venous pressure by the constriction and stretching which we had observed in the axillary vein in the position of hyperabduction and external rotation. The first observation was made with the fluoroscope, after the vein had been visualized with thorotrast. In three patients the emptying time, that is the time required for all the solution to be washed out of the vein, so that it was no longer visible under the fluoroscope, averaged three and a half minutes when the subject was in the recumbent position and the arm was placed at an angle of 45 degrees to the body. When an additional amount (5 cc.) of the solution was injected, after the vein was completely empty, and the arm was immediately hyperabducted and externally rotated, this being the position in which the constriction and stretching of the vein had been noted, there was an almost immediate emptying of the vein, which at the end of thirty seconds showed none of the solution in the part proximal to the point of constriction. It is obvious, then, that instead of a slowing of the venous current occurring in this position, which was previously believed to take place, the emptying time is actually faster than in the approximately normal position of the arm at an angle of 45 degrees to the body.

We passed on, finally, to the question of the venous pressure, the first observation being made with the fluoroscope after injection of thorotrast, with the arm at an angle of 45 degrees to the body. We noted that in this position there was on each normal inspiration a backflow of the opaque solution through the axillary vein and that on coughing or straining this backflow was so much exaggerated that the solution passed backward into the vessels of the arm.

The venous pressure in normal subjects was then measured with the arm in the same position and was found to be just sufficient to force the blood backward through a no. 20 needle, without any overflow. The arm was then raised to a position of hyperabduction and external rotation, a glass tube measuring 100 mm. in length, and of the same bore as that of the needle, having been previously attached to the needle.

This movement was found to cause a rise of about 20 mm., which was, however, momentary, though when the patient coughed or strained the pressure was markedly increased, the blood in some subjects actually overflowing the tube. From these observations it appears that the important factor in raising the venous pressure is not the position of the arm, but rather the increased thoracic pressure which is caused by coughing or straining.

It is, of course, possible that the stretching of the vein which was demonstrated in our fresh autopsy material may cause some damage to the intima of a valve or a tributary, particularly if some anomalous distribution of the tributaries should be present, but this does not seem reasonable. In the four patients whose axillary veins were punctured in our study of the venous pressure there was no clinical evidence of any clot or occlusion following the trauma. Although we found no venous or muscular anomalies in the subjects we observed, such anomalies are notoriously frequent, as Lowenstein has pointed out, and it may be that they are present in the patients in whom thrombosis of the axillary vein occurs. Again, the lack of autopsy material in such cases precludes categorical statements.

#### CONCLUSIONS

Indeed, the conclusion of the whole matter seems to be that some individual variation is the final cause of the accident. James made that point in the discussion of his two cases of thrombosis of the subclavian vein and expressed the belief that this idea of an "idiosyncrasy of anatomic structure" is supported by the fact that nearly all reported cases are observed in right-handed male subjects, in whom the accident occurred through traumatic pressure or pinching of surrounding structures of more than ordinary development. The results of the roentgen and autopsy studies we have reported seem to us to be sufficiently substantiated to be accepted, even though they contradict the results of previous work that has been done. They prove clearly that the constriction of the vein occurs, not as was previously believed over the first rib beneath the subclavius muscle, but below the head of the humerus and against the subcapsularis muscle. The stretching of the vein, the occurrence of which has heretofore merely been assumed, takes place, we have shown, only within the part of the vein just proximal to the point of constriction below the head of the humerus. We have shown that instead of the slowing of the venous current which has previously been assumed to occur, the emptying time is actually more rapid in the position of hyperabduction and external rotation than when the arm is held at an angle of 45 degrees to the body. Finally we have shown that the increase in the venous pressure which has always been

accepted as a causative factor is brought about not by the change of position in itself but only when the additional factor of strain or effort is introduced.

It must be emphasized again, however, that the problem is in no wise solved by the facts we have brought out. The anatomic and physiologic factors we have demonstrated serve merely as contributing causes. Until adequate autopsy material on patients with thrombosis of the axillary vein is available the etiology of the condition must remain speculative, though the most reasonable assumption is that the constant underlying factor is some individual anatomic variation.



Fig. 7.—Roentgenogram showing occlusion of the axillary vein by metastatic carcinoma of the axillary lymph gland. Note the backflow into the cephalic and collateral vessels.

#### OTHER USES FOR VASOGRAPHY

In conclusion we wish to report that in addition to the two cases of primary thrombosis of the axillary vein we have studied by this method, we have also studied four cases of occlusion of the axillary vein caused by tumors of the axillary lymph nodes. In all the latter cases (fig. 7) we were able to demonstrate the site of occlusion and the collateral circulation which had developed after occlusion had occurred. The obstruction is evident as a blockage of the opaque medium, which may flow back into the brachial or even into the cephalic vein. It

seems to us that in cases of malignant involvement of the breast this method should prove valuable in demonstrating the presence of metastatic lymph nodes while they are still impalpable. It may also be of value in demonstrating the presence of mediastinal tumors and other occlusions of the vena cava which cannot be seen by the ordinary roentgen or fluoroscopic examination.

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# CLINICAL STUDY OF THE SPERMATOGENESIS OF UNDESCENDED TESTICLES

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This paper is based on a study of a group of patients with either unilateral or bilateral undescended testicles observed at the Children's Hospital, from 1900 to 1934. During this period 665 cases of cryptorchidism were observed in this clinic. Unfortunately, 186 of the patients have disappeared so that all efforts to reach them over a three year period have failed. Of the remaining 479, 336 have been located, interviewed and examined. Larger series than this have been reported from other clinics, but so far as can be determined all of the investigators have judged the excellence of their end-results on the position and size of the testicle at periods varying from two months to several years after operation. These investigations have been valuable for comparing the various methods of orchiopexy to place and hold the testicle in the scrotum. However, the prime interest in these cases should be centered not on the cosmetic result but rather on the fertility of the patient or the relative fertility in comparison with that of normal persons. The problem of fertility of these persons with cryptorchidism has thus become the basis of this investigation in an effort to throw some light on the spermatogenesis of the testicle for which an orchiopexy has been performed. Naturally, investigations of fertility are impossible until early adult life, so the number of persons available for study in this group of 336 was limited. The present review, which represents only a preliminary report of this work, is based on studies on the fertility in 89 cases from ten to thirty years after operation.

Before considering the fertility of the patient on whom orchiopexy was done one might first review<sup>1</sup> what has been learned and generally accepted about the spermatogenesis of the testicle that remains outside of the scrotum. Experimentally it has been shown in animals that a testicle placed in the abdominal cavity shows evidence of degeneration, but if it is replaced in the scrotum before complete degeneration occurs it will again become apparently normal. If allowed to remain in the abdomen the procreative power of the testicle is lost. It has been shown that testicles removed before puberty, though such instances have been

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From the Department of Surgery of the Children's Hospital, Dr. William E. Ladd, Chief of Staff.

1. Wangenstein, O. H.: The Undescended Testis, Arch. Surg. 14:663 (March) 1927.

few, have been similar in appearance whether they were undescended or not. The undescended testicles that have been removed during the first two to three years after puberty have shown beginning degeneration but with spermatocytes and spermatozoa still present. The greater percentage of retained testicles that have been removed from adults have shown principally the loss of germinal epithelium from the seminiferous tubules and complete absence of spermatozoa. It has thus been generally but not universally accepted that if the undescended testicle is to have spermatogenic power it must be placed in the scrotum before puberty. That this is not always a necessity is shown by the reports of a few isolated instances of fertility in persons with complete cryptorchidism.<sup>2</sup> It has been estimated by one investigator<sup>3</sup> that as high as 10 per cent of undescended testicles show some spermatogenesis. It thus becomes of importance, in order to justify operative procedures in these cases, to prove that in more than 10 per cent of the patients on whom orchiopexy is performed there is fertility and likewise to prove not only the mere presence of spermatozoa but their presence in large enough number to make progeny possible.

Certain operative and nonoperative procedures are available for insuring placement of the testicle in the scrotum. One group advocates leaving the testicle entirely alone in the belief that eventually it will descend into the scrotum before or at the time of puberty. It is impossible to conceive how any one can hold to this theory in all cases. One must encounter at some time the firm, fibrous tissue adhesions of the cremasteric muscle to the structures of the cord, the fibrous tissue blocking the entrance to the small, underdeveloped scrotum, or the testicle that has been reflected upward from the external ring and held in this position by the insertions of the abnormal gubernaculum or adhesions of the associated hernial sac. It is rather incongruous to suppose that at some time in development this fibrous tissue will suddenly disappear and allow the testicle to drop like a plummet into the scrotum. Nevertheless, there is one type of so-called undescended testicle that will descend unaided into the scrotum. This occurs in patients who have an extremely active or short cremasteric muscle. It is not associated with a hernia, and the testicle usually can be brought into the scrotum by manual traction. When traction is released the testicle again recedes into the inguinal canal. The scrotum is better developed in these patients than in those in whom the cord is congenitally short. Therefore it becomes apparent that if the testicle can be

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2. Maréchal, A.: *Thèse de Paris*, no. 307, 1887; quoted by Wangenstein.<sup>1</sup>  
Taylor, A. S.: *Manual of Medical Jurisprudence*, Philadelphia, Lea Brothers & Co., 1886; quoted by Wangenstein.<sup>1</sup>

3. Uffreduzzi, O.: *Dei Pathologie der Hodenretention*, *Arch. f. klin. Chir.* 100:1150; 101:150, 1913.



brought into the scrotum at all it may conceivably descend of its own accord. Of 336 cases in which there has been a periodic follow-up this has been demonstrated to be true in 21. In the same group of 336 cases there were 26 patients on whom an orchiopexy was never performed. In these 26 the testicles could not be brought into the scrotum on the initial examination. In each case the testicle remained in its original position or atrophied to such an extent that it could not be palpated in the inguinal canal.

It thus becomes apparent that the majority of patients need surgical assistance for the proper placement of the testicle. There are four main principles of operative treatment.

Orchidectomy is the procedure reserved for those cases of unilateral nondescent in which the testicle cannot by any method of orchiopexy be placed in the scrotum. In many clinics it is thought to be wiser to remove the testicle rather than to allow it to remain high in the inguinal canal, where it is subject to trauma and causes discomfort. It must also be remembered in this regard that the undescended testicle is more likely to show malignant change than is the normally descended testicle.<sup>1</sup> If the testicle cannot be placed low in the inguinal canal or in the scrotum, where malignant change may be readily noticeable, it is perhaps better to remove it. However, removal should not be done before the patient is 16 or 17 years of age unless the testicle seems to be markedly atrophied before that time. The interstitial cells which supposedly produce the testicular hormones that are linked with the development of the secondary sex characteristics are not destroyed unless the testicle is completely atrophied. If there is any question that the development of the secondary sex characteristics might be retarded owing to the removal of the seat of these hormones it would then seem wiser to attempt orchiopexy rather than orchidectomy on each patient under the age mentioned. If for some reason the testicle cannot be brought down into the scrotum, it should be left in situ, and orchidectomy should be performed at a later date.

The second type of repair is based on the theory that the artery of the vas deferens supplies enough blood to the testicle so that the other vessels of the cord may be cut without impairment to testicular growth. As the vessels are usually the shortest structures of the cord in persons with undescended testicles, proper patience may be lacking to free these structures so that they can be stretched the necessary distance for the testicle to be placed in the scrotum. In every patient in the clinic of the Children's Hospital in whom the vessels were cut the testicle could easily be placed in the scrotum, where it remained without retraction. However, from ten to twenty years after operation every one of the patients treated in this fashion showed

complete atrophy of that testicle. This proves that it is not a desirable operation; in this clinic the result has been poor in every instance.

The third principle of repair comprises freeing of all adhesions of the cord, division of all the cremasteric fibers and freeing of the vessels and vas deferens from the posterior portion of the peritoneum by dissection through the internal inguinal ring. If only the vas deferens and the main arterial and venous trunks are left the cord is usually of sufficient length so that the testicle may be placed in the scrotum without tension. Usually a purse-string suture is placed at the neck of the scrotum to prevent possible retraction. It is to be remembered that this method of repair is based on the theory that with sufficient perseverance the cord can be lengthened. It is thought that to hold the testicle in the scrotum under tension, if lengthening is not adequate, cuts off the blood supply and leads to eventual atrophy. This method of repair, then, does not include fixation of the testicle in the scrotum in any way except perhaps by a temporary stitch to be removed at the end of the operation. It might be said here that this is the type of repair that has been used almost as a routine in the Children's Hospital.

The fourth method of surgical treatment combines the freeing of the cord with fixation of the testicle in the scrotum. Into this division falls the Torek operation and all its modifications. If the Torek operation is used as Torek originally described it (i. e., to free the testicle without injury to the main vessels until it can be placed in the scrotum without tension and then to sew it to the thigh), this fixation becomes effective in aiding the stretching of the underdeveloped scrotum and in preventing retraction of the testicle from scar contracture in the wound itself. It is the opinion in the clinic of the Children's Hospital that if the testicle can be placed well within the scrotum without tension fixation is unnecessary. However, this Torek procedure might well be used in those cases in which in spite of all possible lengthening the testicle will reach only to the upper limit of the scrotum. Such mild traction produced by the Torek procedure in these cases perhaps does impair but does not completely shut off the blood supply. In the modifications of the Torek procedure the tunica or the gubernaculum but not the testicle is usually included in the fixation stitch, and thus further testicular trauma is avoided.

One recent investigator<sup>4</sup> has estimated that there are over forty different operations described to place the testicle in the scrotum. All these methods represent minor variations of the four principles that have been described. It now remains for further investigators in this field to show which of these various methods results in production of

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4. Wolfson, W. L., and Turkeltaub, S. M.: A Modified Torek Operation, *Am. J. Surg.* **25**:495, 1934.

the highest degree of fertility for the patient. However, before discussion of the fertility of persons with this abnormal condition it may be well to review a few of the known factors affecting the fertility of the normal person.

From recent reports it has been shown that the semen of the normal male contains between 100,000,000 and 120,000,000 actively motile spermatozoa per cubic centimeter.<sup>5</sup> Studies of the head, neck and tail of the sperm have revealed that between 8 and 10 per cent may be abnormal in size and shape.<sup>6</sup> Fertility is thought to be greatly impaired if the percentage of abnormal forms reaches 25. Considerable variation from these normal figures is reported in the same person, depending on age, exercise, diet, mental strain, fatigue, the activity of the endocrine glands and, occasionally, the frequency of sexual intercourse. It is thus apparent that one count of the sperm may give a false interpretation of the fertility of that person, as the count in one person has been known to vary from 50,000,000 to 200,000,000 sperm per cubic centimeter during a period of observation. However, unless there is some real pathologic process present the count does not usually go below 50,000,000 sperm per cubic centimeter. It has been generally considered but not definitely proved that an unvarying count of 25,000,000 sperm per cubic centimeter represents the minimum number necessary for fertility, as usually that many spermatozoa are estimated to be destroyed by the vaginal secretions. Instances of proved fertility in persons with counts lower than 25,000,000 per cubic centimeter have been reported,<sup>5a</sup> and the occurrence of such cases is confirmed by this investigation.

#### METHOD OF STUDY

In the study of persons with cryptorchidism, the same technic in making the counts was employed as that advocated by Macomber and Saunders.<sup>5a</sup> The specimens of semen were collected either in a condom during intercourse or in a Petri dish during masturbation. In every instance possible a collection was made by both methods. It was found that the counts of both specimens were almost identical. The counts were made exactly as a white blood cell count except that sodium bicarbonate was used as a diluent, and the total was computed on the basis of a cubic centimeter rather than of a cubic millimeter. Because of the uneven distribution of spermatozoa in the collected specimens three dilutions and counts were made on each specimen, and the results were averaged. Even this did not make the counts absolutely accurate, but they more nearly approached a mean. In all cases of abnormally low or high counts, specimens were collected over a period of time and the results were averaged. In all instances a careful sexual

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5. (a) Macomber, D., and Saunders, M. B.: *The Spermatozoa Count*, New England J. Med. **200**:981, 1929. (b) Belding, D. L.: *Fertility in the Male: II. Technique of Spermatozoa Count*, Am. J. Obst. & Gynec. **27**:25, 1934; (c) *Fertility in the Male: I. Technical Problems in Establishing Standards of Fertility*, *ibid.* **26**:868, 1933.

6. Moench, G. L.: *Am. J. Obst. & Gynec.* **25**:410, 1933.

history was taken so that if extremely low counts were found due consideration and treatment might be given to any factors that might influence the count.

These determinations of spermatozoa were carried out on all the married and unmarried patients over 20 years of age who could be located. Because the investigation involved consideration of an infirmity to which many of them were sensitive it was difficult to persuade them to come in for an examination. The 89 persons on whom studies of fertility were conducted constitute a group made up of 20 persons with complete cryptorchidism and 69 with unilateral cryptorchidism.

#### OBSERVATIONS

The patients with bilateral nondescent of the testicles constituted the most important group for the study of spermatogenesis. It is obvious that no definite conclusions can be drawn from a series of only 20 persons. Interpretation of the results is difficult in a number as limited as this, but it is hoped that this study will stimulate further work in other clinics, so that by grouping the results a true evaluation may be reached.

Of the 20 patients 2 were seen in the clinic and operation was advised but not performed. One was seen at 11 years of age. At that time he had bilateral inguinal hernia, a small left testicle in the inguinal canal and a right testicle of normal size also in the inguinal canal. Orchiopexy was never performed, but a right herniorrhaphy was performed at the age of 20. On examination the patient was 41 years of age. Examination revealed both testicles to be small but in the scrotum, apparently having descended unaided. The patient was married and had three normal children. The other patient was seen in the clinic at 6 months of age. At that time neither testicle could be felt and no hernial sacs were found. At the age of 12 the patient had severe poliomyelitis, which greatly deformed his entire body. At examination the man was 28 years of age and was unmarried. Examination of the testicles revealed that they were normal in size and sensation, but the right one remained low in the inguinal canal while the left was low in the scrotum. The count of spermatozoa was, however, 45,000,000 per cubic centimeter. This is adequate for fertility but is much less than that found in the normal person. It is questionable whether this patient ever had a true cryptorchidism. Examination of the testicles in infancy may be difficult owing to the overactivity of the cremasteric muscle, which on the slightest stimulation may pull the testicle back into the inguinal canal.

There were 3 more patients in the group with bilateral undescended testicles who were seen in the clinic during childhood but were operated on at neighboring hospitals. In 1, examination at 5½ years revealed the left testicle situated in the inguinal canal and the right testicle inside the internal ring. He was operated on at the age of 13, when a left orchidectomy and a right orchiopexy were done. At the time of recent examination the patient was 29 years of age. Examination revealed a man normal in build and development. The left testicle was absent; the right was of normal size, very sensitive, of good tone and in the scrotum. The patient had been married nine years and had no children. No contraceptives were used at any time. The patient had had no venereal disease. Repeated examination of the semen revealed no spermatozoa. The second patient, seen first at the age of 8½ years, had bilateral inguinal hernia and testicles that could be palpated in the inguinal canal but could not be brought into the scrotum. An orchiopexy on the right side was performed in the clinic of the Children's Hospital. The testicle later retracted so that at the age of 14 a second orchiopexy on the same side was done at another hospital. Two years later a herniorrhaphy

and orchiopexy on the left side were performed. At the time of examination the patient was 22 years of age. He was a normal man. Both testicles were of good size and in the scrotum. However, repeated examinations of the semen failed to disclose spermatozoa. These 2 cases illustrate, as will several more, that the cosmetic result cannot be used as an index of fertility. The third patient was first seen in the clinic at 9 years of age, at which time both testicles were normal in size but were situated in the inguinal canal. At 13 years of age a Torek operation was performed on the right testicle, and the left was allowed to remain in the canal in the belief that it would soon descend. The patient was 20 years of age on examination. The left testicle, which was in the canal at the time of the first examination, remained there but was smaller than normal and was less sensitive. The right testicle was well in the scrotum, and remained attached to the lateral wall. This testicle was slightly smaller than normal, but was actively sensitive. The patient was unmarried. Examination of the ejaculatory fluid revealed only 6 or 7 spermatozoa per high power field in an undiluted specimen, too few for counting with the dilution method described previously. If one is to believe that 25,000,000 or more spermatozoa per cubic centimeter are usually killed by the vaginal secretions, this person must be considered essentially sterile. It is, however, still within the bounds of possibility that with artificial impregnation or proper regulation of intercourse he might foster his own progeny. For the purpose of clarity I shall classify this patient as potentially fertile to distinguish him from those of absolute fertility with an adequate sperm count or those of absolute sterility with no sperm.

The remaining 15 patients with bilateral undescended testicles were operated on at the Children's Hospital. With the exception of 2, one 3 years of age and one 5, all were operated on between the ages of 7 and 11. In all these the testicles either were located in the inguinal canal or were intra-abdominal, and in all there was some degree of herniation. Freeing of the cord and, when necessary, retro-peritoneal dissection without fixation of the testicle in the scrotum constituted the method of orchiopexy used. On only one occasion were the vessels of the cord cut. In this instance complete atrophy of that testicle had taken place. On discharge from the hospital at the end of seven or eight days after operation both testicles were in the scrotum in all cases but 1. In this 1 case no testicle could be found on one side. A recent examination revealed that in 10 of the 15 patients both testicles were still well down in the scrotum. Of the remaining 5, 1 patient had only one testicle originally. In 3 there was one testicle, normal in size, well in the scrotum, with the other retracted into the inguinal canal and atrophied to from one-half to one-third the normal size. In the fifth patient both testicles had retracted into the inguinal canal and were markedly atrophied. In addition, this patient had contracted a marked gonococcic infection which finally cleared under prolonged treatment. The combination of these two factors rendered the patient totally sterile. There was no venereal disease in any of the rest of this group.

Of these 15 patients 6 have been married and have had one or more children. Counts of the spermatozoa could not be obtained on all of these persons so as to determine whether they were really the fathers of these children. However, a careful sexual history has led me to believe that they were, although in some, definite microscopic evidence of actively motile spermatozoa is still lacking. In 5 more, as yet unmarried, the counts were 92,000,000, 38,000,000, 50,000,000, 84,000,000 and 38,000,000. This indicates that 11 of 15 patients were definitely fertile. The cases of the remaining 4 need more careful consideration. The first patient was the one mentioned previously in whom both testicles had retracted and atrophied. There were no spermatozoa in the ejaculatory fluid. The second

patient had a routine orchiopexy performed when 11 years of age. When he was 22 examination revealed the right testicle to be normal in size but located in the inguinal canal while the left was normal in size and in the scrotum. Examination of the spermatic fluid on only one occasion revealed no spermatozoa. Repeated attempts to have this person return for a second test have met with no success. I think it is perhaps unfair to classify this patient in the sterile group on the basis of one examination, but until spermatozoa are proved to be present this must stand. The third patient had a routine orchiopexy at the age of 11. He was 22 years of age on examination. Both testes were of normal size and sensation and were well down in the scrotum. Examination of the ejaculatory fluid revealed 4,000,000 sperm per cubic centimeter. The fourth person had a routine orchiopexy at the age of 7. On examination he was 24 years of age. Both testicles were in the scrotum; the left was normal in size and sensation, and the right was slightly smaller and less sensitive. Counts of the spermatozoa repeatedly showed only from 5 to 7 normal spermatozoa per cubic centimeter. The last two patients must be considered essentially sterile on the basis that there were too few spermatozoa. However, even though it seems unlikely on the basis of all scientific data, they probably should be classified as being potentially fertile as long as there is even 1 active spermatozoon in an entire ejaculation.

In summary, among the patients with bilateral nondescent of the testicles there were 3 with no spermatozoa on repeated examination, 1 with none on one examination, 3 potentially fertile with active spermatozoa, but not in adequate number for normal fertility and 13 definitely fertile. Two of the 13 were not operated on; thus there were 11 operative cases of proved fertility. All of the 11 patients were operated on at the Children's Hospital.

The group of patients with unilateral undescended testicle on which studies of fertility have been carried out numbers 69. Seven of these were seen at the Children's Hospital between the ages of 2 and 7. At that time one of the testicles was either in the inguinal canal or in the abdomen. These 7 patients never had an operation performed and returned for examination at ages varying from 20 to 36 years. On examination, in every instance the testicle was found still to be in the inguinal canal and markedly atrophied. Counts of spermatozoa were not done on the married patients, of whom there were 3, as each had had a child. Counts carried out on the 4 unmarried patients were 30,000,000, 50,000,000, 74,000,000 and 133,000,000 per cubic centimeter.

Nine more patients of the 69 seen at the Children's Hospital during childhood were operated on elsewhere. In all instances the undescended testicle could be palpated in the canal on the initial examination. Exact description of the type of operation performed was lacking in some instances. In 3 cases it was known that orchidectomy was done, and in another the vessels were cut. In each, the operation was performed between the ages of 17 and 24. Recent examination revealed the testicle to be absent in the 3 cases in which orchidectomy was done, completely atrophied in 3 more and of good tone and in the scrotum in 3. Four of the patients had children. For 2 of these 4 I have no count, but for the other 2 the counts were 16,000,000 and 26,000,000 per cubic centimeter, respectively. This is interesting in view of the fact that a man with a count of 16,000,000 per cubic centimeter, less than the supposedly required number of spermatozoa, has had three normal children. The counts in the others were 40,000,000, 42,000,000, 49,000,000, 68,000,000 and 104,000,000.

The remaining 53 patients in this series with unilateral undescended testicles were operated on at the Children's Hospital. Nine of them were operated on under 5 years of age and the remainder between 5 and 11. Each patient had an

accompanying hernia. Routine orchiopexy, with retroperitoneal dissection when necessary, was performed on 48 patients. Of the remaining 5, the vessels were cut in 4, and in 1 the testicle was fixed into the scrotum and to the thigh by a silk-worm stitch which was removed at the end of ten days. In all 5 there was marked atrophy of the testicle. In the other 48, on whom routine orchiopexy was performed without fixation, the testicle was in the scrotum in 35 and had retracted back into the canal in 13. Of the 13 in whom retraction had occurred, partial atrophy was present in 4 and complete atrophy in 9. Of the 35 in whom the testicle remained down in the scrotum, partial atrophy was present in 17, complete atrophy in none and a normal testicle in 18. To sum this up from a cosmetic standpoint, we can say that in those cases in which the vessels were cut or the testicle was fixed in the scrotum the result was poor. Approximately 30 per cent of the patients having routine orchiopexy had a poor result in that the testicle retracted and atrophied completely or in part. In the remaining 70 per cent the testicle was well in the scrotum.

The relative fertility of these patients is much harder to evaluate since one testicle was originally normal in size and position. It was thought impossible to catheterize the ducts and to collect separate specimens from each testicle during ejaculation. The count of spermatozoa thus becomes less valuable as an index of absolute fertility in this group. It is of paramount interest to discover not whether these persons are fertile but whether they are normally fertile when the testicles appear to be normal (i. e., to be well descended and equal in size). It is also of interest to know if the fertility is measurably diminished in persons in whom there is complete atrophy of one of the testicles. Of this group of 69 patients with unilateral undescended testicle, 21 have had children. Counts of spermatozoa were done on 54, and in only 3 instances were there less than 25,000,000 per cubic centimeter. One patient had had a repeated gonococcal infection which was arrested at the time of the test. Repeated specimens showed no spermatozoa. Examination of the testicles revealed the left to be normal and the right, which had originally been undescended, now in the scrotum, but only one-half the size of the left. In the second case the testicles appeared to be normal in size and position. Cosmetically the result was excellent. Repeated counts over a period of eighteen months showed only from 6 to 10 sperm per high power field in an undiluted specimen. In the third case only one test was done. At that time there were only 2,000,000 sperm per cubic centimeter in the specimen and yet this patient had three normal children. He was 44 years old, and all three children had been born during his early thirties. For the four years preceding examination no contraceptives had been used, yet the man married for a second time and wished to have children by the new union. It is entirely possible that fertility has reached a definite period of decline and that further progeny might be impossible. Further studies will be carried out in this case at definite intervals to see if there is any further measureable decrease.

Except for these 3 patients whose counts were low the remaining 51 showed counts varying from 25,000,000 to 175,000,000 per cubic centimeter. In only 3 was the count over 100,000,000. In these 3 the testicles appeared to be normal, and in 1 there seemed to be three testicles. In the patients in whom there appeared to be excellent results the counts ranged the entire scale. The counts for the patients in whom one testicle was atrophied also varied from low to high. Consequently one is led to infer one of two things: either that atrophy of one testicle does not materially affect the fertility of that individual or that the count of spermatozoa is not an accurate enough factor with which to measure relative fertility. I must tend to the latter view, because I believe the method used in

testing these patients is subject to too many mechanical errors in collection, dilution and count. The future study of relative fertility will then have to depend on a more accurate method of counting. However, the present tests on the patients with unilateral cryptorchidism have been uniform in consistently showing that except for 3 high counts, all of the specimens collected were below normal, 50 per cent of the counts being below 50,000,000 per cubic centimeter.

#### SUMMARY

A résumé of the fertility of persons with normally descended testicles has been made so that it will serve as a standard on which to compare the data for the persons with undescended testicles. The methods of orchiopexy have been reviewed. The studies of fertility of 89 men with undescended testicles have been compiled in an attempt to determine their fertility or relative fertility. Because the series is too small and the mechanical index too variable for evaluation of relative fertility one can draw only three definite conclusions:

1. Except in a small percentage of cases the fertility of all persons with cryptorchidism seems to be lower than that of the normal person. The same type of investigation and method of counting has been used in both groups.

2. The cosmetic result after orchiopexy cannot be used as a criterion of fertility.

3. In 18 patients with bilateral undescended testicles on whom orchiopexy had been done, there was definite fertility in 11, and in 3 more, in whom the counts were lowered but active sperm were present, potential fertility. The percentage of definite fertility in persons who have undergone orchiopexy may then be computed as 61 per cent in contrast to the estimated 10 per cent in persons without orchiopexy. If one is to add the 3 cases in the group with potential fertility, the percentage is raised to 77. In my opinion these statistics definitely make orchiopexy a justifiable procedure.

My main purpose in this paper has been to stimulate an interest in other clinics to carry out a similar type of investigation. I hope this will be fulfilled. I intend to continue the investigation and at a later time will report on a larger series in which something more definite can be offered in correlation of the types of orchiopexy with the resulting spermatogenesis.

NOTE.—Since this paper was submitted for publication more patients with bilateral undescended testicles have been found and examined and counts of their spermatozoa have been made. All 4 were seen and operated on at the clinic of the Children's Hospital between 4 and 9 years of age. At the initial examination in each case both testicles were found in the inguinal canals with an accompanying herniation. At recent examination their ages varied from 21 to 26 years. In all



instances both testicles were well in the scrotum and normal in size, shape and sensation. None of the men are married or have had children, but the counts on their ejaculatory fluid were 30,000,000, 30,000,000, 46,000,000 and 60,000,000.

If this group is added to others reported in the article the total percentage for proved fertility in these abnormal cases is raised from 77 to 82 per cent.

## CYSTIC HYGROMA OF THE NECK

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Cystic hygroma of the neck is a comparatively rare condition and generally appears in children under the age of 5. It does, however, occur in adults, and my report includes the case of a patient 37 and another of a patient 18. Dr. Charles N. Hyatt reported two cases in which this condition occurred in adults, one patient being 19 and the other 20 years of age. It is usually present at birth or occurs sufficiently soon after birth to indicate that the condition is probably a developmental error. Arnold,<sup>1</sup> who studied this condition most thoroughly as far back as 1865, concluded that a congenital defect was the underlying cause. Thompson and Keiller,<sup>2</sup> in 1923, almost conclusively proved the following theory of origin to be true: In the 6 week embryo, the development of the lymphatic system is begun with the formation of the so-called lymph sacs, four in number, two being located between the carotid and the subclavian artery, one on either side, and two in relation to the iliac arteries. The main outgrowths of the first two mentioned form the lymph channels of the head, the neck and the arm; those of the other two, the lymph channels of the lower extremities and of the pelvis. The primitive lymph sacs later atrophy. Independent of this system, small islands of lymphoblastic cells are formed which develop into lymph vessels, later joining the larger system. This development probably takes place not only throughout intra-uterine life but during the subsequent first two years of the child's life. It is feasible to conclude from this description that hygroma may originate in the persistence of the primary lymph sac, in an offshoot of the sac or as a result of an island's detaching itself from the rest of the lymphatic system. Its final development may occur a few years after birth because its ancestral lymphoblasts were of the slower developing variety. It is possible for hygroma to develop in any region where the original lymphoblastic material is laid down. Clinically, it occurs most commonly in the cervical and axillary regions, rarely in the groin and almost never elsewhere. When hygroma involves deep structures of the neck or

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From the New York Post-Graduate Medical School and Hospital, Columbia University.

1. Arnold, Julius: *Zwei Fälle von Hygroma colli cysticum congenitum*, Virchows Arch. f. path. Anat. **33**:209, 1865.

2. Thompson, James E., and Keiller, V. H.: *Lymphangioma of the Neck*, Ann. Surg. **77**:385 (April) 1923.

of the axilla, it is because lymphatic tissue was previously laid down in that region and the cysts pushed their way out, rather than because the peripheral cysts dissected their way in. A cyst follows the path of least resistance, which is to the surface. To date, no specific cause has been found for the existence of hygroma; it is undoubtedly a lymphangiectasis. The most satisfactory explanation of the existence of cystic hygromas is that embryonic sequestrations of lymphatic tissue existed and that they had the power of persistent irregular growth.

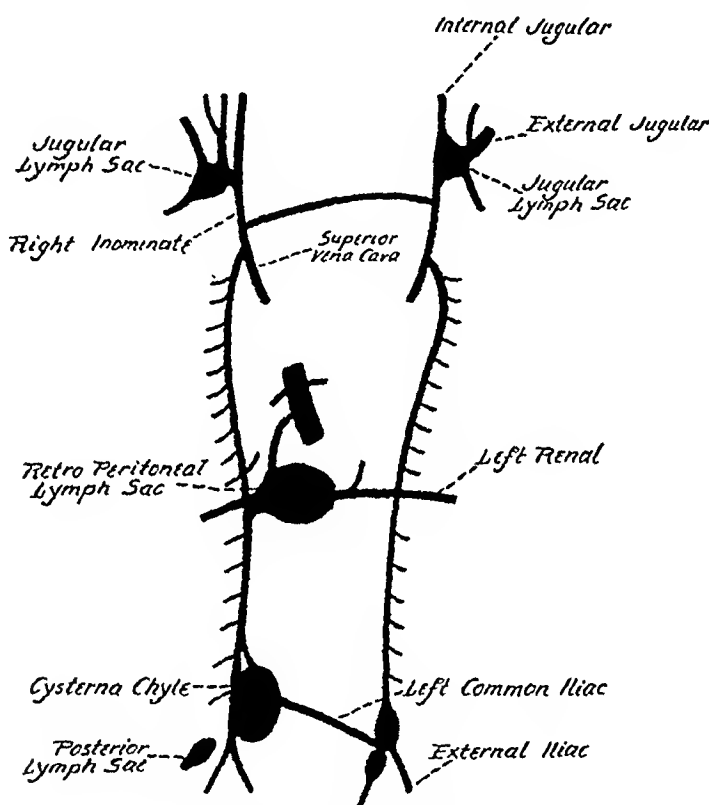


Fig. 1.—Schematic drawing showing the principal lymph sacs in their relation to the vascular system.

The term cystic hygroma of the neck should be restricted to thin-walled cysts lined with endothelium containing a serous fluid and having a marked power of growth. The cyst may be single or multilocular, and it may attain very large size. The endothelium is made up of a single layer of cells having the appearance of a mosaic. Any rapid increase in the size of the tumor is due to an increase in the lymph content, since no evidence of increased cell division has been shown nor does other evidence of malignant tissue exist. Hygroma of the neck usually is situated immediately lateral to the carotid sheath and anterior to the cervical nerve roots. It often extends down under the clavicle for a short distance, lying on the pleura. In his comprehensive report

of all cases on record to 1913, which totaled ninety-one, Dowd<sup>3</sup> described one case in which the growth practically covered the upper part of the left side of the chest anteriorly. At operation, the cysts lay beneath the pectoralis major muscle, almost completely enveloping the pectoralis minor muscle and extending under the clavicle of the neck beneath the subclavian vessels. In the cases reported by Dowd, forty patients were definitely cured, the treatment for most of them being total operative excision, and thirty-nine died. Hyatt<sup>4</sup> was not able to find more than sixteen cases of hygroma of the neck reported over the period from the time of Dowd's report in 1913 to 1932. In Hyatt's review of cases, two patients, one 19 years of age and the other 20, had cystic hygroma of the neck of from six to twelve months' duration.

In seventeen cases of cystic hygroma of the neck from the New York Post-Graduate Medical School and Hospital, the variation of age was rather marked. In this series of patients, the condition predominated in men. The history of sudden increase in size of the cyst lasting for two or three days, followed by sudden decrease, was noted. In several instances the cyst was aspirated by a physician outside the hospital, undoubtedly for the purpose of diagnosis since it assuredly could not have been for radical cure.

In case 6 of the series that I am reporting, a serious swelling followed an aspiration performed at another hospital. Consequently, the patient was admitted to the New York Post-Graduate Medical School and Hospital in a critical condition. The cyst was of the multilocular variety and was extensive.

#### REPORT OF CASES

The last operation performed on a patient with this condition in the New York Post-Graduate Medical School and Hospital took place on Nov. 3, 1934. Dr. Charles G. Heyd performed the operation. A detailed report of the case follows:

CASE 1.—S. L., a girl 16 months old, was admitted to the hospital on Oct. 20, 1934. She had a tumorous growth about two-thirds the size of an orange on the right side of her neck over the right clavicle between the ramus of the mandible and the clavicle, as shown in figure 2. The overlying skin was movable and not inflamed. The mass could be punctuated but was not tender. It was of two months' duration and had appeared first as a small lump which gradually had increased to its present size.

Physical examination showed the child to be normal in every respect, and the family history was not contributory. The child had never had a contagious or

3. Dowd, Charles N.: Hygroma Cysticum Colli: Its Structure and Etiology, *Ann. Surg.* 58:112 (July) 1913.

4. Hyatt, Charles N.: Hygroma Cysticum Colli: A Case Report with a Review of the Literature, *J. Iowa M. Soc.* 22:406 (Aug.) 1932.

infectious disease prior to the examination. About two weeks previous to the date of admittance the patient had been examined by another physician, outside the hospital, who had aspirated about 15 cc. of a dark red fluid from the tumorous mass.

Laboratory tests of the blood and of the urine showed both to be normal, except for the presence of many bacteria and a few squamous epithelial cells in the urine.

The preliminary diagnosis was a multilocular cyst or a cystic hygroma of the neck.

Röntgen examination showed a large, soft tumor in the right cervical area, of smooth contour and of homogeneous consistency and apparently without definite osseous connection. It resulted in a slight elevation and deviation of the laryngeal shadow. No gross pathologic change in either pulmonary field was observed. The conclusion was that a large, soft tumor existed in the right cervical area.

On November 3, Dr. Charles G. Heyd excised the tumor by operation. The operation was entirely uneventful and proved successful.



Fig. 2.—Showing cystic hygroma on the right side of the neck. The mass contained clear fluid and was lined with endothelium.

The patient had an uneventful recovery from the operation. She rested, slept and ate well. A slight serous discharge was noted on the dressing for the first two days following the operation. The child was rather listless until the morning of November 6, when there was a profuse purulent drainage, after which she seemed to be brighter and started to use her right arm without apparent difficulty. A comfortable convalescence continued until her discharge from the hospital on November 12. The patient returned to the hospital later for examination and was found to be in excellent health, the wound having healed nicely.

*Pathologic Report.*—The specimen measured in its collapsed state 60 by 50 by 30 mm. It consisted chiefly of an incised cyst the contents of which had been evacuated. The wall of the cyst was of fibrous tissue from 2 to 3 mm. in thickness. Its inner surface was smooth and pale gray except for fine white or reddish streaks. One portion of the wall of the cyst was thickened by fibrous tissue and fat which were adherent to the outer surface. On section, this portion of the wall contained cystic areas filled with coagulated opaque jelly suggesting mucus. Between these cystic spaces, there was fat, and covering the surface in this area there were tabs of muscle.

*Microscopic Examination.*—Sections through the walls of the various cysts presented the same picture. The cysts were lined by one or two layers of flattened cells, which in a few areas were cuboidal with pink-staining cytoplasm. The underlying stroma was formed in part of fairly young fibroblasts running in various directions and in part of myxomatous tissues. About scattered capillaries there was lymphocytic infiltration, fairly abundant in some areas. In the deeper layers of the wall, there were blood vessels with sclerosed walls and cross-sections of fairly large nerve trunks. The proliferation of fibrous tissue extended in delicate strands into the surrounding fat, where occasional capillaries were surrounded by lymphocytes. In some areas, the lymphocytic infiltration was marked throughout the wall. The content of the cyst was a mixture of mucus and albumin, and only one or two mitotic figures were seen in the entire section examined.

*Diagnosis.*—The condition was diagnosed as a multilocular cyst with associated chronic inflammation, especially fibrosis.

The following review includes some of the most interesting cases of this condition in patients treated in the New York Post-Graduate Medical School and Hospital.

CASE 2.—M. S., 14 years of age, noticed a swelling which appeared on the right side of the neck two years before consultation. It remained stationary for six months and then suddenly became markedly increased in size.

The pathologic report, dictated by Dr. Paul Klemperer, recorded the measurements of the specimen as 120 by 20 mm. The histologic picture showed a few large cavities which were empty and lined throughout with endothelium.

The next case represents an instance of the early occurrence of the condition.

CASE 3.—C. M., 1 month old, was admitted to the hospital on Aug. 31, 1922. There was a swelling on the right side of the neck which had been present since birth. It had grown larger continually. As illustrated by figure 3, it occupied the entire space between the mandible and the right clavicle. The cyst had grown into and penetrated the sternocleidomastoid, the digastric and the mylohyoid muscle. It was excised in toto from the submaxillary region, but there was a prolongation along the carotid vessels which extended posteriorly into the muscles in the back of the neck that made it impossible to dissect out the cyst cleanly. The cavity was treated with phenol successfully.

This case was particularly interesting because it showed how these cysts or their prolongations can penetrate or push through other structures. It also demonstrated the impossibility of a clean dissection, especially in the multilocular variety of cystic hygroma of the neck when it has invaded the mediastinum.

CASE 4.—A boy, aged 1½ years, was brought to the hospital by his mother, who first noticed a swelling on the right side of his neck when he was 3 weeks old. It had been growing larger almost constantly. Operation revealed a multilocular cyst extending up to the internal jugular vein, which made operative removal very difficult. It was totally excised.

CASE 5.—J. L., a boy  $4\frac{1}{2}$  years old, presented a tumor on the right side of the neck. The swelling was first noticed two and a half years before consultation and had gradually increased in size.

The collapsed cyst measured 3 cm. in length and 1.5 cm. in diameter and was lined with endothelium.

CASE 6.—L. G. was a girl aged 4 years and 3 months. About three and a half months previous to the patient's admittance to the hospital the mother noticed a small lump on the right side of the child's neck. For a period of three or four weeks, it remained the same size. It then began to enlarge and steadily grew in size until the operation, which was performed at another hospital on Oct. 5, 1927. Following the operation, the tumor grew much more rapidly than before. Two weeks after the operation, it was aspirated and a bloody serum was obtained. The child was admitted to the New York Post-Graduate Medical School and Hospital on Nov. 24, 1927. The tumor was completely excised, and the wound healed nicely.



Fig. 3.—Showing cystic hygroma of the neck and of the chest.

The fibromembranous mass measured 7.5 by 4 by 1.3 cm. and contained numerous opened cavities which appeared to communicate with each other. The cavities were lined with endothelium.

CASE 7.—I. H., a girl 18 years old, for a year previous to her admittance to the hospital had noticed a small lump on the right side of her neck which had increased gradually to the size of a hen's egg. For a period of two or three days, it would increase very much in size and then would decrease slowly to its original size. An operative excision was performed and two pieces of membrane, the one 45 by 25 mm. and the other 40 by 8 by 8 mm., were removed.

CASE 8.—F. L., a man 36 years old, for three years previous to his examination at the hospital had noticed a swelling on the right side of his neck which gradually had increased in size. It was about 2 inches (5 cm.) in diameter and, at times, greatly increased in size. The tumor was removed by operative excision. It was a thin-walled cyst and measured 32 mm. in diameter and less than 1 mm. in thickness.

I have reviewed in this series not only a few cases which illustrate the usual characteristics of this condition but some which presented unusual surgical complications. Since the tumor arises in a region of the body which is interspaced with a complicated maze of important blood vessels, nerves and muscles, it is of paramount importance that the physician, before attempting to treat this complication, thoroughly acquaint himself with the nature of the various phases of the condition and the region in which it occurs.

#### CONCLUSIONS

The unfamiliarity of the medical profession in general with the condition known as cystic hygroma of the neck is rather surprising, to say the least. Its importance to the surgical clinician is apparent since it must be considered when a differential diagnosis of the surgical conditions of the neck is being made. The prognosis must be very guarded in the cases of the multilocular variety. Thorough removal is the ideal procedure in the case of a unilocular cyst or in the case of the multilocular variety, when it is not very extensive.

Radical operative procedure is not to be considered when roentgenograms reveal that the multilocular cyst extends across the neck and down to the mediastinum, especially when the cyst has been aspirated and a 15 per cent solution of an iodized poppy-seed oil which has been diluted with poppy-seed oil is injected. For this condition, there is the choice of two treatments: (1) repeated aspirations, which must be performed under strict aseptic conditions to avoid contamination which might prove fatal and followed by the injection of a sclerosing fluid such as sodium morrhuate, which was used by Harrower<sup>5</sup> in the successful treatment of this condition in one of his cases; (2) roentgen therapy after first reducing the size of the cyst by aspiration, as recommended by Figi.<sup>6</sup>

Early diagnosis and radical operation when the cyst is small would avoid serious complications later.

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5. Harrower, Gordon: Treatment of Cystic Hygroma of the Neck by Sodium Morrhuate, *Brit. M. J.* 2:148 (July 22) 1933.

6. Figi, Frederick A.: Radium in the Treatment of Multilocular Lymph Cysts of the Neck in Children, *Am. J. Roentgenol.* 21:473 (May) 1929.



# BACTERICIDAL EFFECT OF HIRUDIN AND HEPARIN

## I. INTRAVENOUS INJECTION OF HIRUDIN AND OF HEPARIN AND LEECHING IN EXPERIMENTAL BACTEREMIA

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AND

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NEW ORLEANS

Interest in leeches has been revived by the reports of excellent results obtained from their use in the treatment of phlebitis by Termier,<sup>1</sup> Sulger and Bozsán,<sup>2</sup> Mahorner and Ochsner<sup>3</sup> and others. Attention given to the active substance, hirudin, secreted by these annelids is opportune, since the reports on the results of this method of treating phlebitis continue to confirm its value and injections of hirudin offer a possible substitute for the application of leeches, which evoke a feeling of revulsion in the patient.

In a previous paper we discussed the action of hirudin and called attention to the report by Bosc and Delezenne<sup>4</sup> on experiments undertaken to determine whether hirudin exerted any bactericidal effect on micro-organisms. They found that hirudinized blood produced precipitation of *Bacillus coli* in vitro more effectively than the same amount of blood not hirudinized. In vivo experiments were undertaken by the same authors. After injections of sufficient hirudin to render the total volume of blood incoagulable, at subsequent intervals of from fifteen to forty-five minutes they injected into the blood stream of the animals lethal doses of colon bacilli or streptococci. The control animals died promptly, but the hirudinized animals recovered.

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1. Termier, J.: Grenoble-Abortive Treatment of Surgical Phlebitis with Early Leaving of Bed, *Procès-verbaux et mém., Cong. de chir.* **31**:49, 1922; Grenoble-Abortive Treatment of Surgical and Obstetrical Phlebitis Through Hirudinization (Application of Leeches), *Compt. rend. Cong. de chir., Paris*, 1925, p. 434.

2. Sulger, E., and Bozsán, T.: Ueber die post-operative Thrombose und Embolie sowie ihre therapeutische und prophylaktische Behandlung mit Blutegeln, *Deutsche Ztschr. f. Chir.* **216**:175, 1929.

3. Mahorner, H. R., and Ochsner, A.: The Use of Leeches in the Treatment of Phlebitis and the Prevention of Pulmonary Embolism, *Ann. Surg.* **98**:408, 1933.

4. Bosc and Delezenne: Imputrescibilité du sang rendu incoagulable par l'extrait de sangsue, *Compt. rend. Acad. d. sc.* **123**:465, 1896; De l'immunité conférée par quelques substances anticoagulantes. De son mécanisme: excitation de la phagocytose, augmentation du pouvoir bactéricide du sang, *ibid.* **123**:500, 1896.

We became interested in this subject because of our clinical observations concerning the use of leeches in the treatment of phlebitis. The report of Bosc and Delezenne<sup>4</sup> stimulated us to investigate the possibility of a protective action of hirudin against bacteremia.

Because, as we discussed in our former article, the beneficial effects in the treatment of phlebitis with leeches may be attributed possibly to the softening of the clot by an anticoagulant and possibly to the antagonistic action on the inflammation, we used in the present investigation another anticoagulant, heparin, partly as a control and partly as a possible substitute for hirudin in the treatment of phlebitis. Hirudin at \$150 a gram was almost prohibitive for clinical use or experimentation on a large scale. Heparin differs from hirudin in its action on blood in the following particulars: It is obtained from liver and is found in small quantities in the circulating blood. According to Howell,<sup>5</sup> it reacts with prothrombin so as to prevent its activation into thrombin. However, heparin as well as hirudin is nontoxic to the animal organism in quantities sufficient to prevent coagulation of the drawn blood. Shionoya<sup>6</sup> stated that 1 mg. of heparin renders 100 cc. of human blood incoagulable for twenty-four hours or more, and that from 20 to 25 mg. of heparin per kilogram of body weight administered to animals prolongs the clotting time to from thirty minutes to several hours. Though it is not known exactly how hirudin acts, it is thought by Howell<sup>5</sup> to react with thrombin so as to prevent the latter's action on fibrinogen. Barratt<sup>7</sup> shared this view of the anticoagulant effect of hirudin, but Bodong<sup>8</sup> thought that hirudin acted as an antifibrinogen, and Gratia<sup>9</sup> believed it to be an antithrombin and Arthus,<sup>10</sup> an anti-prothrombin. However, not one of these theories completely explains the action of hirudin on blood. When a few cubic centimeters of blood is allowed to clot in a test tube and a few milligrams of hirudin is sprinkled in, the blood becomes fluid again.

For our *in vivo* experiments we used forty-one dogs. There were fifteen controls in which bacteremia was induced by the method described

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5. Howell, W. H.: The Purification of Heparin and Its Presence in the Blood, *Am. J. Physiol.* **71**:553, 1925.

6. Shionoya, T.: Studies on Experimental Partial Thrombosis; Effects of Certain Anticoagulants (Heparin and Hirudin) on Extracorporeal Thrombosis and on Mechanism of Thrombus Formation, *J. Exper. Med.* **46**:19, 1927.

7. Barratt, J. O. W.: Anticoagulant Action of Hirudin, *Brit. J. Exper. Path.* **7**:127, 1926; Action of Hirudin upon Thrombin, *J. Physiol.* **64**:47, 1927.

8. Bodong, A.: Ueber Hirudin, *Arch. f. exper. Path. u. Pharmacol.* **52**:242, 1904-1905.

9. Gratia: Mécanisme de l'action anticoagulante de l'hirudine. La neutralisation réciproque de l'hirudine et de la thrombine, *Compt. rend. Soc. de biol.* **83**:311, 1920.

10. Arthus, quoted by Barratt.<sup>7</sup>

herewith. No hirudin or heparin was given. In eleven dogs bacteremia was induced, and intravenous injection of heparin was given. In eight dogs bacteremia was induced, and leeches were applied to the skin. In one dog bacteremia was induced, and hirudin was injected intravenously. In three dogs used as controls hirudin was injected intravenously, and in three more dogs used as controls leeches were applied to the skin.

#### METHODS

*Production of Bacteremia.*—The suspension of bacteria injected intravenously into the dogs to induce bacteremia was obtained in the following manner: The forty-eight hour growth on meat infusion agar plates (Petri dishes) inoculated with staphylococci was suspended in physiologic solution of sodium chloride in the proportion of twelve plate cultures to approximately 3 ounces (60 cc.) of solution of sodium chloride. This suspension was injected intravenously into the dogs, each animal receiving 0.5, 1, 2, 4 or 8 cc. per kilogram of body weight. With this dose it was hoped that among controls receiving injections of the suspension alone the dogs receiving the larger doses would die and those receiving smaller doses would live. Temperatures were recorded before inoculation and at subsequent periods of from one hour to three days. They were observed after that, but no records of temperature were made after the first three days.

*Treatment of Bacteremia with Leeches or Hirudin.*—Five leeches were applied to each of eight dogs into which the suspension of staphylococci had been injected intravenously. Two of the dogs received 0.5 cc. of the bacterial suspension per kilogram of body weight; two, 1 cc.; two, 2 cc.; one, 4 cc., and one, 8 cc. In addition, one dog receiving 4 cc. of the culture per kilogram of body weight was given 21 mg. of hirudin intravenously. About 7 mg. of hirudin may be extracted from one leech. It is assuming too much, however, to consider that when a leech is applied and sucks its fill it delivers its entire hirudin content into the systemic circulation.

*Treatment of Bacteremia with Heparin.*—Heparin in solution, a dose of 30 mg. per kilogram of body weight, was injected intravenously into eleven dogs in which bacteremia was induced at the same time by an intravenous injection of the suspension of staphylococci. Two of these dogs received doses of 0.5 cc. of the suspension per kilogram of body weight; two, 1 cc.; two, 2 cc.; two, 4 cc., and three, 8 cc. Each of the dogs had a control which received an identical dose of the staphylococcus suspension but no heparin.

*Treatment of Controls with Heparin and Leeches.*—Thirty milligrams of heparin per kilogram of body weight was injected intravenously into each of three dogs, and five leeches were applied to the skin of the abdominal wall of each of three other dogs. These six dogs were used as controls.

#### RESULTS

The results are stated briefly in the table.

*Controls.*—The three dogs to which heparin alone was given and the three dogs to which leeches alone were applied all lived and showed no untoward effects. As we had hoped, the dose of staphylococcus suspension was so selected that those dogs receiving a minimum dose usually lived while those receiving the severe and moderate doses died.

Thus, of the fifteen dogs into which staphylococci alone were injected intravenously, four lived. The fifteen dogs were divided into three series. Thus three dogs received 0.5 cc., three, 1 cc., three, 2 cc., three, 4 cc., and three, 8 cc., of the suspension of bacteria per kilogram of body weight. The dogs that survived were the three that received

*Results of Experiments on Dogs with Intravenous Injections of Hirudin and of Heparin and with Leeches*

Dog	Dose of Staphylo- coccus Suspension, Cc. per Kg.	Number of Leeches	Dose of Hirudin, Mg. per Kg.	Dose of Heparin, Mg. per Kg.	Died	Lived	Group Results
1	0.5	..	..	..	Killed on 18th day		Mortality, 60%; average survival, 56 hours
2	1	..	..	..	Killed on 18th day		
3	2	..	..	..	49 hr.	..	
4	4	..	..	..	96 hr.	..	
5	8	..	..	..	24 hr.	..	
6	0.5	5	..	..	28 hr.	..	Mortality, 100%; average survival, 34 hours
7	1	5	..	..	122 hr.	..	
8	2	5	..	..	12 hr.	..	
9	4	5	..	..	12 hr.	..	
10	8	5	..	..	3 hr.	..	
Second Group							
11	0.5	..	..	..	Killed on 8th day		Mortality, 80%; average survival, 27 hours
12	1	..	..	..	60 hr.	..	
13	2	..	..	..	36 hr.	..	
14	4	..	..	..	12 hr.	..	
15	8	..	..	..	1 hr.	..	Mortality, 80%; average survival, 60 hours
16	0.5	..	..	30	8 days (pneumonia)		
17	1	..	..	30	Killed on 8th day		
18	2	..	..	30	36 hr.	..	
19	4	..	..	30	12 hr.	..	
20	8	..	..	30	½ hr.	..	
21	..	5	..	..	.....	Lived	No mortality
22	..	5	..	..	.....	Lived	
23	..	5	..	..	.....	Lived	
24	..	..	..	30	.....	Lived	
25	..	..	..	30	.....	Lived	
26	..	..	..	30	.....	Lived	
Third Group							
27	0.5	5	..	..	.....	Lived	Mortality, 50%; average survival, 29 hours
28	1	5	..	..	29 hr.	..	
29	2	5	..	..	29 hr.	..	
30	4	..	21	21	.....	Lived	Mortality, 100%; average survival, 91 hours
31	8	..	..	30	12 hr.	..	
32	0.5	..	..	30	5 days	..	
33	1	..	..	30	5 days	..	
34	2	..	..	30	6 days	..	
35	4	..	..	30	31 hr.	..	
36	8	..	..	30	5 days	..	Mortality, 80%; average survival, 49 hours
37	0.5	..	..	..	.....	Lived	
38	1	..	..	..	5 days	..	
39	2	..	..	..	29 hr.	..	
40	4	..	..	..	12 hr.	..	
41	8	..	..	..	36 hr.	..	

0.5 cc. of the suspension and one that received 1 cc. Since each of these dogs represented a control for a dog treated with heparin or with leeches or both, they will be considered in more detail with the series for which they were controls.

*Treatment with Heparin.*—In the first series of five dogs treated with heparin four (80 per cent) died, having an average length of life of

sixty hours, whereas of the five control dogs for this series four (80 per cent) died, having an average length of life of twenty-seven hours.

In the second series of dogs treated with heparin all six dogs died (100 per cent). The dog which survived longest lived six days, and the average duration of life of the series was ninety-one hours: Of the five controls for these six dogs (two of the six dogs treated with heparin received the same dose of the bacterial suspension) four died (80 per cent). The average duration of life of the four was forty-nine hours. All of the deaths occurred within five days.

The temperatures of the control animals showed very little difference from the temperatures of animals treated with heparin either when those of individual dogs treated with heparin were compared with those of their individual controls at different periods of time after injection or when averages were used of all the temperatures of an individual dog up to eighty-four hours or of the temperatures of all the dogs in the series at a definite period after injection. For all the dogs in the series except those which received large doses and died almost immediately there was a definite rise of temperature within two hours after injection to between 101 and 105 F. The fever gradually subsided after from twenty-four to forty-eight hours in the dogs that recovered.

Therefore, of the eleven dogs receiving heparin intravenously at the time bacteremia was induced only one lived, the mortality being 90.9 per cent. Two of these dogs had the same dose of the same culture and had only one control. There were thus only ten controls. Of these ten dogs two survived, the mortality being 80 per cent. The dog treated with heparin that survived was one that had received a small dose of the staphylococcus suspension, 1 cc. per kilogram of body weight. The control dogs that survived had received only a minimum dose of the suspension, 0.5 cc. per kilogram of body weight.

It might be concluded from these results that injections of heparin given intravenously do not protect an animal against a staphylococcic bacteremia.

*Treatment with Leeches and Hirudin.*—Of the first series of five dogs treated with leeches all died (mortality 100 per cent). The longest survival was one hundred and twenty-two hours, and the average length of time they survived was thirty-four hours. Three of the five control dogs in which bacteremia was induced died (60 per cent). All three deaths occurred within ninety-six hours, and the average length of time three dogs survived was fifty-six hours.

In the second series treated with leeches there were three dogs. One survived and two died (mortality 66.6 per cent). Both deaths occurred at the end of twenty-nine hours. Of the controls for these three dogs treated with leeches two died and one survived (mortality 66.6 per cent):

The average length of time the two dogs survived was seventy-four hours after receiving injections.

One dog received 21 mg. of hirudin intravenously at the same time that it received 4 cc. of the bacterial suspension per kilogram of body weight. This dog survived. Its control, receiving a similar dose of staphylococci but no hirudin, died in twelve hours. Moreover, it was the only dog receiving so large a dose of the bacterial suspension in the entire experiment that survived. From this fact alone no conclusion can be drawn.

Twenty-one milligrams of hirudin is the approximate amount which may be obtained from three leeches and is sufficient to render incoagulable only 150 cc. of blood. It is far less than the amount which must have been used by Bosc and Delezenne in their experiments, when they rendered the entire blood volume of their animals incoagulable. We are anxious to repeat this part of the experiment using hirudin intravenously in larger doses.

The temperature reaction in the dogs treated with leeches and in their controls was similar, but the average was a little higher in the control dogs than in those to which leeches had been applied.

It is obvious that leeches do not protect the animals from staphylococcic bacteremia, since of eight dogs treated with leeches seven died (87.5 per cent), whereas of the eight controls only 5 died (62.5 per cent). From our result it would appear that leeching increases the mortality. Doubtless a large, if not the entire, factor is the loss of blood. Each leech may suck approximately 15 cc., and some additional blood is lost from oozing. So each of the dogs treated with leeches lost a quantity of blood. This may explain in some measure the discrepancy of our results from application of leeches and intravenous injection of hirudin. The question is still unsettled from these experiments whether hirudin exerts a protective effect. Although this is possible and even suggested by the *in vivo* experiments, it would seem from the *in vitro* experiments that it has no such synergistic action on the responses of the defense mechanisms of the blood as was claimed by Bosc and Delezenne.<sup>4</sup>

*Necropsy.*—In those animals that died within a few hours after injection nothing was found at autopsy to account for the death, which must have occurred from an overwhelming toxemia.

In the animals that died in from twelve hours to two days small hemorrhages were found in the lungs, spleen and kidneys. In those animals dying after three days abscesses were found usually in the kidneys and sometimes in the lungs. In the subcutaneous tissue of the abdomen of some of the dogs to which leeches had been applied were found large ecchymoses.

## SUMMARY

In order to determine the effect of leeches applied to the skin, of hirudin given intravenously and of heparin given intravenously on bacteremia, experiments were undertaken, forty-one dogs being used. Into thirty-five of the dogs a suspension of staphylococci was injected intravenously, each dog receiving one of five different doses, 0.5 cc., 1 cc., 2 cc., 4 cc. or 8 cc. per kilogram of body weight. Into three dogs used as controls heparin alone was injected intravenously, and to another three used as controls leeches alone were applied. Of eight dogs receiving leeches in addition to injections of the bacterial suspension intravenously seven died (87.5 per cent), whereas of their eight controls receiving analogous doses of the staphylococcus suspension but no treatment with leeches five died (67.5 per cent). Thus apparently leeching is an added factor in the production of death.

One dog received 21 mg. of hirudin intravenously in addition to a large dose of the bacterial suspension. This animal recovered and was the only one in the entire series receiving so large a dose of staphylococci that did recover. No conclusion is drawn. The discrepancy of the results obtained by leeching and by intravenous injection of hirudin may be due to the loss of blood by the former method.

Of eleven dogs receiving heparin intravenously in addition to the suspension of staphylococci ten died (90.9 per cent). Of their controls 80 per cent died. Thus heparin injected intravenously does not assist an animal in overcoming bacteremia and is apparently an added factor in increasing the mortality.

## CONCLUSIONS

The application of leeches to dogs in which bacteremia has been induced increases the mortality. Hirudin injected intravenously may have some beneficial effect.

Heparin injected intravenously into dogs with staphylococcic bacteremia increases the mortality.

## A REVIEW OF UROLOGIC SURGERY

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### KIDNEY

*Anomalies.*—Wiseman<sup>1</sup> expressed the opinion that before operation is undertaken for the relief of obstructive effects of a congenital anomalous formation of the urinary tract it is of the utmost importance to make a thorough and searching urologic study. According to Hunner, too many single kidneys have been removed on the assumption that the patient possessed a second kidney. It is important to determine beforehand the presence or absence, as well as the degree, of infection in the kidney which is to be subjected to a plastic procedure, the functional status of the involved organ and the possibility of bilateral involvement. A congenital urinary anomaly is a potential source of obstruction and of subsequent urinary stasis and infection. Anomalous blood vessels in close proximity to the upper third of the ureter, although not actually responsible for the collapse of the ureter, may, by their pulsations, interfere with the normal flow of the peristaltic wave down the ureter, and thereby promote stasis and pyelectasis. In the absence of demonstrable obstruction at the ureteropelvic juncture, or of the ureter, in a group of cases in which the condition was classified as being of idiopathic origin, Walters was able to demonstrate a subepithelial fibrosis at the pelvic outlet and occasionally faulty or lateral insertion of the ureter into the pelvis, which he regards as the contributing factor. The obstruction may be relieved by division of adhesions that

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1. Wiseman, J. L.: Congenital Urinary Anomalies: An Evaluation of the Associated Obstructive Syndrome with Report of 6 Cases, *Ann. Surg.* **100**:445 (Sept.) 1934.



cause the angulation of an accessory ureter, or by division of an anomalous blood vessel. Unless the aberrant vessel is extremely small it should not be severed, because it is an end artery and its division really amounts to partial nephrectomy. It is possible to determine beforehand the vascular supply of the kidney which will be affected by division of an aberrant vessel, by temporary clamping with a rubber-covered hemostat. When the caliber of the vessel is too large to permit division without seriously affecting the blood supply of a large portion of the kidney, the ureter may have to be severed from the hydronephrotic sac and reimplanted at another point. Whenever there is a large redundant sac, resection will have to be performed in such a way that the ureteropelvic juncture at the conclusion of the operation occupies a position at the most dependent portion of the sac. The measure of success or failure of plastic and other conservative procedures for the correction of hydronephrosis and the contributory ureteral obstruction may be gaged by the alleviation of symptoms, by the pyelographic evidence of decreasing capacity of the sac, and by the return of its functional capacity as estimated by differential functional renal tests and, less accurately, by the density of the dye that is excreted following intravenous excretion urography.

Sangree, Morgan, Klein and Trasi<sup>2</sup> reported that symmetrical horseshoe kidney most commonly fuses by the lower pole, constituting the long kidney. It rarely fuses by the upper pole. Various degrees of dystopia and inclination to one side or the other may occur, represented by the "caked" kidney, the "sigmoid" kidney and the "L-shaped" kidney; these are classed as asymmetrical types. Fused kidneys are more commonly the seat of pathologic changes than are normal kidneys, especially those changes that are incident to urinary stasis. Before instituting surgical procedures for the treatment of horseshoe kidneys, the surgeon should consider the possibility of anomalous vessels, often multiple in number and variable in position. A wedge-shaped arrangement of calculi in a urogram should arouse suspicion of the presence of a fused kidney. Concomitant congenital anomalies should always be investigated in the study of a horseshoe kidney. In every case in which there is an abdominal mass and the triad of umbilical or lumbar pain, gastro-intestinal disorders and urinary disturbances, horseshoe kidney should be considered.

*Stone.*—Prather<sup>3</sup> said that nephrotomy is necessary at times in order to remove large branching calculi without sacrificing the kidney.

2. Sangree, Henry; Morgan, David; Klein, Thomas, and Trasi, Rocco: *Horseshoe Kidney and the Relation of Nephritis and Calculous Formation to Anomalous Circulation: A Report of Twenty-Five Cases*, J. Urol. **32**:648 (Dec.) 1934.

3. Prather, G. C.: *A Method of Hemostasis During Nephrotomy for Large Kidney Calculi*, J. Urol. **32**:578 (Dec.) 1934.

Operations which involve a large portion of the cortex of the kidney have rightfully been considered serious procedures, principally because of these four factors: (1) primary hemorrhage; (2) sepsis in the cortex of the kidney; (3) destruction of functioning tissue by the cortical incision or suture, and (4) secondary hemorrhage.

Pressure on the pedicle in one form or another for hemostasis during operation has been suggested by a number of operators. Manual compression between two fingers is objected to because the hand used in this manner may be in the way of the operator, and the fingers, acting as compressors, tire frequently and interrupt the surgeon. Temporary clamping of the pedicle is an effective method, which is easily applied, gives instantaneous control, and does not interfere with the operative field. However, care must be taken that the clamp shall not injure the walls of the vessels of the pedicle, and that the temporary anemia produced by clamping of the pedicle shall not be harmful to the kidney. Kummel described a featherweight metal clamp for this use. Prather uses a semiflexible Doyen curved intestinal clamp, which is 9 inches (22.8 cm.) long, covered with soft rubber boots, and shaped so that in closing the clamp pressure is applied last in the middle of the blades. This clamp is applied to the pedicle after the ureter has been separated and retracted. The ureter is not included in the clamp. No damage to the vessels of the pedicle has been observed in cases in which such a clamp has been applied just tightly enough to produce hemostasis. The clamp has been released for from twenty to forty seconds at the end of eight minute to ten minute periods of compression, in order to allow the flow of blood through the kidney to be temporarily resumed.

In cases in which there are large branching calculi which form a cast of the kidney, with additional small stones, which sometimes occur in calices with narrowed infundibula, the accepted procedure, exclusive of nephrectomy, apparently has been a full length sagittal incision through Brödel's white line. This region has been falsely called an avascular area. In Prather's cases in which there were stones of the stag-horn type, he made a V-incision on the posterior surface of the kidney, with the apex of the incision at the pelvis, and with the ends of the incision extending toward each pole and over the stone. With a small retractor lifting the flap of cortex, the stone may be completely visualized and easily removed in one piece, without breaking off fragments. This incision is shorter than a full length sagittal one of the same kidney, and is made easily and quickly by placing the incision directly over the stone. By this method, more than half of the kidney is not touched by the incision or the sutures. After the stone has been removed, openings to all the calices are within sight, in a bloodless field, so that they may be explored easily if roentgenologic examination of the wound indicates remaining calculi. Hemostasis and adequate

exposure permit rapid, yet careful, removal of stones from a kidney. After roentgenologic examination has shown that there are not any remaining calculi, and a bougie has been passed down the ureter into the bladder to insure its patency, the nephrotomy incision is closed with 00 chromic catgut. A no. 18 F. Pezzer catheter is placed so that it emerges from the end of the incision at the lower pole. This should remain in place for from fourteen to sixteen days. The rapid rate of healing and postoperative pyelograms indicate that there is not any necrosis of the V-section of renal tissue.

Secondary hemorrhage can be diminished by placing the sutures close to the line of incision in order to avoid large infarcts and by always draining the kidney with an adequate nephrotomy tube. Irrigation through this tube is often advisable in order to keep the kidney free from clots.

With due regard for the futility of always doing extensive nephrotomy rather than nephrectomy, Prather expressed the opinion that at times it is inadvisable to remove the kidney. Nephrotomy is especially indicated in cases in which the patients are so-called "stone-formers," and in cases in which there are large stones in both kidneys. This procedure has made it possible to avoid nephrectomy without undue risk.

Prather reported a group of consecutive cases in which there had not been any secondary hemorrhage, and included reproductions of roentgenograms which were made before and after the operation.

Barney and Mintz<sup>4</sup> reported on a group of 18 patients who had hyperparathyroidism, which was proved by operation, 11 (61.1 per cent) of whom also had calculi in the urinary tract. These 11 patients are included among 104 with calculous disease previously reported on, giving a total of 10.5 per cent who had disease of the parathyroid gland. There are other patients in this group who may prove to have hyperparathyroidism, thus increasing this percentage considerably. These 11 patients who had urinary calculi, together with 7 others who did not have any calculi but who did have cystic degeneration of the bone, have all been operated on, the cases forming, in the opinion of the authors, a unique series. In most of the cases in which there was lithiasis, the parathyroidectomy followed the lithotomy.

Of the 18 patients, 12 (70 per cent) were females. The youngest patient was 13, and the oldest was 62 years of age, with an average age of 43 years. The value for the calcium varied from 11.5 to 16.8 mg. per hundred cubic centimeters of serum, with an average of 13.78 mg.; the value for the phosphorus averaged 2.55 mg. per hundred

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4. Barney, J. D., and Mintz, E. R.: Some Newer Conceptions of Urinary Stone Formation, *Tr. Am. A. Genito-Urin. Surgeons* 27:203, 1934.

cubic centimeters of serum and ranged from 1.4 to 4.7 mg. A value of more than 11 mg. per hundred cubic centimeters for the serum calcium and a value below 3.5 mg. for the serum phosphorus should always be an indication for investigation. Involvement of bones, ranging from large, multiple cysts to simple decalcification, was found in 12 cases (70.5 per cent). In 6 cases, urinary calculi and bony changes were found together. The stones were bilateral in 4 (36 per cent) of the 11 cases, and the urine was normal in 35 per cent of the cases. There was no operative mortality.

A careful reexamination of as many as possible of their patients who had urinary lithiasis and who were subjected to operation for removal of the stones has been instituted. To date 33 patients have been examined. The examination included quantitative estimation of the calcium and phosphorus in the serum and roentgenologic examination. Eleven ( $33\frac{1}{3}$  per cent) of these 33 patients revealed the high value for the serum calcium which is so consistent with parathyroid disease.

Albright and Bloomberg<sup>5</sup> reported that hyperparathyroidism is so frequent a cause of the formation of stone in the urinary tract that it must be determined whether or not it is present in every case of this disease. Eleven cases are cited from a series of 23 proved cases of hyperparathyroidism at the Massachusetts General Hospital in which the presence of renal stones was the only indication that led to the diagnosis of the underlying disease. A frequent finding in cases of hyperparathyroidism is many finely granular casts in the urinary sediment. The granules have been shown to contain calcium, probably calcium phosphate. The casts can be made to change into hyaline casts as the urine is made more acid by the administration of ammonium chloride by mouth. Their continuous presence in large numbers is an indication that intrarenal damage is in progress. The factors governing the formation of these casts, which in a way are microscopic calculi in the renal tubules, are probably the same as those which govern the formation of stone in cases of hyperparathyroidism. These factors are the concentrations in the urine of calcium, phosphate and hydrogen ions. The formation of stone in cases of hyperparathyroidism belongs to that etiologic group in which the predisposing abnormal factor is an excess of crystalloids in the urine. This fact is justification for further attention to this line of approach in the solution of calculosis in general.

Keyser,<sup>6</sup> in discussing etiology of stone, said that he was successful in producing an excessive excretion of calcium oxalate in the urine of

5. Albright, F., and Bloomberg, Esther: Hyperparathyroidism and Renal Disease with a Note as to the Formation of Calcium Casts in This Disease, *Tr. Am. A. Genito-Urin. Surgeons* 27:195, 1934.

6. Keyser, L. D., in discussion of Joly, J. S.: Etiology of Stone, *J. Urol.* 32:575 (Dec.) 1934.

rabbits by simultaneous subcutaneous injections of butyl oxalate and calcium chloride. The first appearance of oxalate crystals in the urine revealed their morphology as that of isolated octahedrons. With intensification of the excretion, there appeared spherical crystals, which had a tendency to agglutinate, fuse and form stones. According to the laws of crystalline precipitation from colloidal solutions, Keyser demonstrated that the urinary colloids would carry a certain amount of oxalate in solution. A further saturation resulted in the deposition of isolated octahedral units, while an excretion of amounts beyond the power of the colloids to deposit isolated crystals resulted in colloidal inadequacy; as a consequence, there fell from solution crystals of spherical form in such profusion that they became agglutinated to form concrements. Previous work with calculi, which were produced by the feeding of oxamide, had suggested a similar mechanism of hyperexcretion calculus. This appeared to involve also a certain amount of deposition of urinary pigment in the forming stone. It was shown that experimental production of stasis augmented the deposition of stones when carried out in conjunction with the production of such crystalline hyperexcretion.

In the reports of a high incidence of calcium phosphate calculi associated with hyperparathyroidism, Keyser observed a clinical confirmation of the existence of a hyperexcretory type of formation of stone. The excessive excretion of calcium phosphate and its deposition as stone in cases of hyperparathyroidism markedly parallel the excessive excretion of calcium oxalate observed in experimental animals. Various observers noted intense phosphaturia, deposition of salts in the uriniferous tubules and nephritis. Likewise, Keyser found in animals an identical type of nephritis with deposits of oxalate crystals in the renal tubules. In this connection is cited the belief that uratic calculi are the result of excessive excretion of uric acid, and that uric acid tubular infarcts, which have been noted in infants, may be associated with stone.

Higgins<sup>7</sup> stated that in the experimental production of stones in rats by employing diets that were deficient in vitamin A, three constant findings were observed: (1) infection, (2) persistent alkaline urine and (3) keratinization or metaplasia of the epithelium of the renal pelvis, ureter and bladder. He is convinced that the infection was not the sole factor in the production of the stones. The incidence of infection did not keep pace with that of formation of stones in the early stages of the experiments. If ammonium chloride is added to the diet, tending to acidify the urine, it is more difficult to produce calculi. The chemical factors involved in the experimental production of stones may now be satisfactorily explained to satisfy the requirements stressed by colloidal

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7. Higgins, C. C., in discussion of Joly,<sup>62</sup> p. 236.

chemists, and it unquestionably is true that the high alkalinity of the urine and keratinization of the epithelium are the important factors. Higgins expressed the opinion that vitamin deficiency disease is not the cause of all calculi, as lithiasis also is found associated with metabolic disease. There are also cases in which calculi are associated with hyperparathyroidism. Experimentally, calculosis can be produced in the parenchyma of the kidney by injection of parathyroid extract, but it has not been possible to produce stones in the pelvis of the kidney or in the bladder. It is only by careful interpretation and analysis of all the experimental work and correlation with all clinical observations that it may finally be possible to find a single etiologic factor associated with all calculous disease.

Lower<sup>8</sup> reported that it has been definitely proved experimentally that stones can be produced by depriving animals, particularly rats, of vitamin A, and that by restoring this vitamin to the diet, many of these stones disappear, according to roentgenographic evidence.

In applying this knowledge clinically, a diet rich in vitamin A has been prescribed for patients who have been subjected to operation for stones in the ureter or kidney. A small series of patients who had renal calculi and who refused operation or who had bilateral lithiasis have been receiving a special diet which is rich in vitamin A and which produces an acid ash. In each of 2 instances, a small stone in the lower calyx of the kidney, too large to pass spontaneously, has disappeared within four months, according to roentgenographic examination. In 2 cases, multiple large bilateral renal calculi have decreased definitely in size within thirteen months. One of the patients did not pass sand or calculi in the urine until she had taken the special diet for three months; the urine is now continually filled with sediment and small stones. Another patient had a large stone which completely filled the left kidney. In the six months during which he has taken the diet that is rich in vitamin A and productive of an acid ash, 323 small calculi have been passed. Previously, the patient never had passed sand or a stone in the urine.

Barney<sup>9</sup> said that at the Massachusetts General Hospital 104 patients who have had stone have been examined for parathyroid disease by an estimation of the calcium and phosphorus in the serum. A value of more than 11 mg. per hundred cubic centimeters for the serum calcium and a value below 3.5 mg. per hundred cubic centimeters for the serum

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8. Lower, W. E., in discussion of article by Joly, J. S.: Etiology of Stone, *J. Urol.* **32**:570 (Dec.) 1934.

9. Barney, J. D., in discussion of article by Joly, J. S.: Etiology of Stone, *J. Urol.* **32**:573 (Dec.) 1934.

phosphorus should always arouse suspicion. Eleven (10.5 per cent) of these patients were found to have hyperparathyroidism. These 11 patients, together with 7 others who had no stone but who had other manifestations of the disease, such as bone cysts and decalcification, were all operated on, and the parathyroid tumor removed. There was no operative mortality, although a patient died in the hospital, a month after operation, from uremia which was the result of the extensive renal destruction induced by the disease. Twelve (70 per cent) of these 18 patients were females. The ages varied from 13 to 62 years, the average being 43 years. Bony changes consisting of cysts or decalcification were found in 12 (70.5 per cent) cases. In 6 cases stones and changes in the bones occurred together. The urine was normal in 35 per cent of the cases. Bilateral stones occurred in 36 per cent of the cases.

A careful reexamination of all the patients who had a stone in the urinary tract is being undertaken by Barney. Thirty-three patients have been examined, which included not only routine physical examination and urinalysis, but also study of the blood chemistry and roentgenologic examination. In 11 patients the values for the serum calcium and serum phosphorus indicated hyperparathyroidism. Further examination of these patients will be made with this in mind. In only 2 instances were bony changes found at roentgenologic examination.

Priestley<sup>10</sup> reviewed 500 cases of renal calculosis and obtained data on types of calculi encountered, types of operations performed and pathologic changes associated with renal calculi. Unilateral stones were present in 85.2 per cent of the cases and bilateral stones in 14.8 per cent. There was about an equal division between multiple (55 per cent) and single (45 per cent) stones. In 10.4 per cent of the cases, calculus of the ureter was associated with nephrolithiasis. Treatment for these calculi varies, depending on the size of the ureteral stone, its situation in the ureter, the amount of infection present and the degree of ureteral dilatation.

Of these 500 patients, 8.6 per cent were operated on for recurrent calculi. The incidence of recurrence of renal calculi following their surgical removal has been variously estimated at from 8 to 40 per cent. Judd and Scholl found a recurrence in 10.4 per cent of 1,024 cases.

Of the various surgical procedures used in these cases, pelviolithotomy was performed in 44.6 per cent of the series; nephrolithotomy, in only 3 per cent. In recent years, pelviolithotomy has supplanted

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10. Priestley, J. T.: Surgical Aspects of Renal Calculi, Proc. Staff Meet., Mayo Clin. 9:486 (Aug. 15) 1934.

nephrolithotomy as the operation of choice for removing renal calculi. The former procedure is safe, is easily performed, and is followed by excellent end-results. Nephrostomy was performed in 17.4 per cent of these cases. Priestley expressed the opinion that the more widespread use of nephrostomy, as advocated by Cabot, has done more than anything else in aiding to rehabilitate kidneys which previously would have been considered irreparably injured. Multiple operative procedures were carried out in 26.2 per cent of the cases. In this group are the more complicated cases, which include partial resection of the kidney, division of a horseshoe kidney, associated ureterolithotomy, combined pelvonephrolithotomy and nephrostomy. Nephrectomy was necessary in 26.2 per cent of cases.

Unilateral stones were removed in 95 per cent of cases, and bilateral, at a single admission, in 5 per cent. Operations may involve the kidney and ureter on the same side with less risk than when both sides of the urinary tract are involved. In general, it seems desirable to remove large branched bilateral renal calculi, because otherwise they usually lead to progressive renal injury and may demand emergency surgical treatment later. The entire mortality in the 500 cases of renal calculus was 2.3 per cent.

Various pathologic changes were found associated with renal calculi. Congenital anomalies were noted occasionally (5 per cent) and consisted of anomalous renal vessels, duplicated renal pelves, fused kidneys and ectopic kidneys. Generally, these conditions did not appear to be instrumental in the formation of calculi, unless the anomaly caused obstruction. Hydronephrosis, either moderate or marked, occurred in 61 per cent of cases. Although some hydronephrotic sacs were sterile, as in the case of a "primary stone," the renal pelvis frequently exhibited moderate inflammatory changes. In cases of pyonephrosis (10.6 per cent) infection was severe, and the kidney often changed to a densely adherent, thick-walled sac, filled with pus. A subcapsular type of nephrectomy is employed frequently in these cases. Kidneys with reduced function were noted in some cases (19 per cent), and in others (7.8 per cent) there was no function.

Cumming<sup>11</sup> said that the problem of treatment of bilateral calculi of the kidney and ureter is involved to a degree which makes the application of regular principles of procedure to all cases entirely impossible. Patients who have stones on both sides of the urinary tract are often seriously ill when first examined; they are always potentially so, and

11. Cumming, R. E.: Treatment of Bilateral Renal and Ureteral Calculi, *J. Urol.* 32:600 (Dec.) 1934.



caution should be exercised. The results of routine tests to determine function, the presence of infection and the relationship of these factors to potential recovery of the kidney are not always borne out while the patient is under treatment. Conservatism will give the greatest satisfaction and tends to provide a longer period of life and comfort for the patients.

Cumming reviewed the general opinions of urologists on the subject of bilateral calculi, adding his personal comments. He expressed the opinion that certain generally accepted principles of treatment are not basically sound in spite of their long usage. His beliefs are based on experience and the work of many colleagues who agreed with him in the principles which he adopted years ago and have been satisfied with their clinical results.

The results of treatment and the follow-up records in a series of 43 cases provide evidence in favor of the procedure which has been outlined by Cumming. However, each individual case should be considered on its own merits, proceeding with the idea of saving the patient's life by preserving as much renal tissue as possible. Acceptable treatment also includes a constant study of all factors influencing the cause of primary stones and recurrences, and attempts to apply preventive treatment. Accessory factors, such as focal infection and ineffectual drainage, must be recognized and handled properly.

De Illyes<sup>12</sup> said that cases of renal calculus have increased enormously since the war, especially in countries where living conditions have been poor. His article is concerned only with the recurrent formation of stones in kidneys that had previously been subjected to operation.

It often is difficult to distinguish between true recurrent calculus and pseudoformation of calculi, for even if every traceable stone has been removed, there may be other minute ones remaining that were hidden by larger stones in the roentgenogram. Again, small pieces may become detached at operation and remain anchored in spite of the utmost care. There also may be minute stones or a gritty substance which is not revealed by the roentgenogram and which escapes detection during the operation. Another cause may be found in the operative technic; otherwise, there would be no explanation of the fact that the statistics of some surgeons reveal a great number of recurrences while those of others do not. Such conditions are not to be considered as true recurrences. Following 510 operations of the conservative type (pyelotomy, ureterotomy), there were 49 recurrences, of which 42 (7 per cent) were true recurrences and 7 were pseudorecurrences; 5 of these followed nephrotomy, and 44 followed pyelotomy and ureterotomy.

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12. de Illyes, Geza: Des calculs rénaux récidivants, *J. d'urol.* **38**:419 (Nov.) 1934.

In de Illyes' statistics the percentage of recurrences after pyelotomy is somewhat higher than that of recurrences after nephrotomy since he was forced in most cases to remove the stone through the pyelotomy wound, a method of stone removal which is less dangerous than nephrotomy, even when severe perinephritis is present. Drainage in such cases is established by continuous catheterization of the ureter or by transrenal drainage.

Stones may be so opaque at times as to show no shadow or only a very vague one in the roentgenogram. In a case in which the stone was later immersed in water and then photographed, hardly anything was visible. This stone was found to consist of pure urate. This explains how easily a stone may remain in the kidney if its situation cannot be established beforehand.

It is possible now to take a roentgenogram of an exposed kidney by placing under the organ a film in a specially constructed and sterilizable case. The rigidity of the case, however, prevents a photograph of the whole organ. Therefore, Illyes recommended that the film be wrapped in dark paper, then in sterilized tin-foil or in a thin rubber sheet. This flexible film-pack is then placed under the kidney and permits roentgenography of either the whole organ or only the desired parts. In case any hidden stones are revealed, the operation may then be continued. This means of control is of great service.

Other important points in prevention of a recurrence of stone formation are: 1. The arrest of hemorrhages. If this is not possible, transrenal drainage and subsequent irrigation are necessary. 2. During pyelotomy, the renal pelvis must be sufficiently uncovered, and the incision should be extended to the renal parenchyma. After pyelotomy, a few stitches are helpful, even in cases of infection, if an indwelling catheter has been inserted. Care must be taken that the sutures do not touch the cavity of the renal pelvis. Furthermore, the kidney must be fixed sufficiently high.

Three causes of true recurrence of calculi may be mentioned: infection, retention and diathesis.

Infection always has been known as a major cause. Lately, it has been demonstrated that a number of bacteria may precipitate the colloids from the urine, and that they then serve as a nucleus around which phosphates and carbonates build up stones. Among the infectious bacteria, the staphylococci play the largest rôle by decomposing the urine. Ammonia is formed and the urine is thus rendered alkaline; this in turn favors the formation of calculi.

Retention is the accumulation of urine in the pelvis of the kidney or in the calices. It is sometimes difficult to determine whether the stone causes the retention or whether retention caused the formation of the

calculus. The most serious cases are those in which branched coral stones distend the intrarenal part of the renal pelvis and the calices, for even after removal of the stone a cavity remains, and the rigid wall of this cavity can maintain retention and encourage recurrence. In such cases, nephrectomy is always indicated if the other kidney is unaffected or only slightly affected. Cases in which only one or two calices are enlarged by retention are more favorable for operation than those with enlargement of all the calices, and recurrence of stone is less likely if a kidney which is uncovered at operation is not fixed fairly high. Another preventive measure is the removal of parts of a dilated renal pelvis.

The third factor of recurrence consists in diathesis during certain periods of life. Judd, Parker and Morse, therefore, expressed the opinion that recurrence is the result of the fact that the end of such a period has not arrived. They advised against renewed operative measures before the end of this period. But since most such operations are urgent, it unfortunately is rarely possible to postpone them. Braasch and Foulds also supported the hypothesis that formation of stones will persist until chemical balance is again attained. Although different diets can be prescribed for patients suffering from stones that are caused by uric diathesis, oxalic diathesis or excessive excretion of phosphates, the cause of the diathesis and of the formation of calculi still remains obscure. Attempts at dissolving stones in the organism have been partly successful, as demonstrated in cases in which there are stones in the bladder, either primarily formed or recurring after prostatectomy. While there are no chemical means known as yet for dissolving or reducing stones, their recurrence may be discouraged by an appropriate diet and by employing means to dissolve uric acid.

Herman and Greene<sup>13</sup> expressed the opinion that anuria with acquired single kidney is rare and less fatal if properly treated than are other types of obstructive anuria. Calculous anuria seldom occurs after nephrectomy for conditions other than calculous pyonephrosis; it is rare if the remaining kidney is normal at the time of the original operation. It is prone to occur after nephrectomy has been performed in cases in which there is cystinuria. In the majority of cases the indwelling catheter should be employed to overcome the anuria in preparation for removal of the obstructive stone or stones. Certain small calculi of the ureter, especially if impacted in the lower part of the ureter, may be removed by cystoscopy. The primary purpose of operation is to establish free urinary drainage. This may be done by operation on

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13. Herman, L., and Greene, L. B.: Calculous Anuria in Acquired Single Kidney, *J. Urol.* **32**:623 (Dec.) 1934.

the kidney or on the ureter, as circumstances dictate, but primary ureterolithotomy is especially indicated in cases in which there are large stones in the ureter. In cases in which the condition is serious and especially in those in which the patients have been operated on previously, nephrotomy, with or without removal of the obstructive stone or stones, is the method of choice. In the majority of cases, the obstruction can be removed without too much damage to the kidney.

*Tumors.*—Geschickter and Widenhorn<sup>14</sup> expressed the opinion that most renal tumors may be related to stages of development of the permanent kidney. In spite of the difficulty in demonstrating the remains of embryonic nephrogenic tissue in the more slowly growing malignant nephromas and in the nephrogenic zone of the opposite kidney, comparisons of the structures of Wilms' tumor, the benign and malignant cystadenomas and the more rapidly growing malignant nephromas of young adults indicate that all of these nephrogenic tumors have their origin in a similar mother substance. Judging from the microscopic studies, this tissue of origin is the renal blastema, a compact group of spindle cells which differentiate into small tubular structures, composed of oval epithelial-like cells. This type of primitive tissue or renal blastema predominates in Wilms' tumors of children, the spindle cells being more prominent than early tubule formation. Among the benign and malignant cystadenomas of young adults, spindle cells and small tubules composed of oval epithelial cells predominate in many of the growths, particularly those which have undergone malignant change. In the nephromas, which affect elderly patients, the blastemic elements are difficult to demonstrate in all but the more malignant and rapidly growing tumors, but do occur. In the three groups of tumors taken as a whole, not only does the shift from immature spindle to adult epithelial forms appear to represent the cycle of growth within the individual tumor, but the extent of maturity reached, as shown microscopically by scarcity or prevalence of large epithelial elements, can be correlated definitely with the age incidence of the tumor and its relative degree of malignancy. The fact that all of these neoplasms show a distinct tendency to make their appearance just beneath the capsule in the normal growth zone of the kidney and the fact that the cortical zone of renal tissue normally continues to grow until adult life relate all of the growths to a single type of developing tissue. Consequently, the present study seems to indicate that the variations in structure which have been regarded as making for separate types of tumor are the expression of the various rates of growth and the extent of differentia-

14. Geschickter, C. F., and Widenhorn, Hans: Nephrogenic Tumors, *Am. J. Cancer* 22:620 (Nov.) 1934.

tion achieved by the individual form of tumor rather than an indication of origin from separate and distinct tissues.

Randall<sup>15</sup> said that the embryonic character of renal tumors in infancy and childhood permits one to expect a marked diminution in their size from adequate roentgenotherapy. Such irradiation cannot be expected to be completely curative, that is, to destroy completely all neoplastic cells. Recurrences after irradiation exhibit increased resistance to this form of therapy, and ultimately the new growth exceeds irradiative destruction, that is, becomes "fast" to any type of irradiation. The fact that the consultant surgeon does not see these lesions early, owing to the latency of the symptoms, renders their operative removal both hazardous and at times impossible. Preoperative irradiation not only decreases this operative hazard but, by the decrease in size, minimizes the additional danger of manipulative and traumatic spread of malignant cells. The choice of time for operation, after the completion of thorough irradiation, appears to be between the fourth and the sixth week. There is no detriment to prompt healing in operating at this interval after irradiation. Those applying the radiation have learned the importance of watching the leukocytic count during the course of treatment. In some patients a leukopenia develops which is considered an evidence of lowered resistance and, if marked, contraindicates further irradiation at that time. Preoperative irradiation should include the thorax and abdomen, in an effort to create an unfertile field for metastatic transplants that may be dislodged in the handling of the tumor at the time of extirpation. Three cases in which the patient was treated by this method are reported.

In the first case described, the patient was treated in 1928, and the optimal time for operation was unavoidably missed. Death occurred subsequently from metastasis. In the second case, although the lesion was explored and considered inoperable, it was nevertheless rendered operable by irradiation, and nephrectomy was later performed easily. The patient was cured, but two years after the operation death occurred as the result of bronchopneumonia. A most complete necropsy proved the absence of the neoplasm. The third patient was in excellent health nine months after the operation; the specimen failed to show the presence of true malignant cells, though the preoperative study left no doubt of the existence of the tumor and its rapid disappearance under irradiation. As a result of the experiences of the past, this could not be taken as a cure, any more than the casually taken microscopic sections from this specimen could be taken as an indication of the absence of isolated nests of malignant cells elsewhere in the specimen.

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15. Randall, Alexander: Advantages of Pre-Operative X-Ray in Kidney Tumor in Children, *Ann. Surg.* 100:462 (Sept.) 1934.

Sinkoe, Fowler and Berger<sup>16</sup> reported a case of Wilms' tumor of the kidney, and cited certain facts which verify the findings of other clinical investigators. A diagnosis should be made as early as possible and proper therapy immediately instituted. Early operative intervention offers the best prognosis. If the tumor is found to encroach on adjacent vital structures, the outlook is not favorable, because of surgical shock and the frequency of recurrence. The curative value of roentgenotherapy and radium therapy is questionable when they are used alone; however, in conjunction with surgical treatment, they may be of considerable value.

Shupe<sup>17</sup> expressed the opinion that tumor of the pelvis of the kidney is rare when compared with neoplasm of the renal parenchyma. Such tumors comprise about 7 or 8 per cent of all tumors of the kidney and are classified into two main groups, the papillary and the solid growths. The papillary tumors may be benign or malignant. The sessile growths consist of the transitional cell carcinoma and the squamous cell carcinoma. The papillary tumors are the most numerous, occurring in about 75 per cent of the cases of tumor of the pelvis of the kidney. Among 337 cases collected by Joly, there were benign papillomas in 120 cases, papillary carcinomas in 138 cases, transitional cell carcinomas in 29 cases and squamous cell carcinomas in 50 cases. The papillomas, whether benign or malignant, usually are multiple, are extremely vascular and bleed readily. This type progresses by extension to the calices, ureter and bladder. The solid tumors grow and extend by invasion of the renal vein and perirenal tissues. They metastasize remotely to the lungs, liver and bones.

The symptoms are those of any tumor of the kidney, of hydronephrosis or of calculi. This fact, plus their rare occurrence, is why tumor of the renal pelvis is seldom diagnosed before intervention. Hematuria occurs in about 90 per cent of all cases in which there are papillary tumors and in 50 per cent of cases in which there are non-papillary growths of the kidney.

Albarran found 8 growths of the bladder in 25 cases in which there was a tumor of the renal pelvis. Paris found 5 tumors of the bladder in 37 cases in which there was a tumor of the kidney. Occasionally, a polyp will almost completely block the orifice of the ureter, leading to hydronephrosis and a rapid development of the growths in the pelvis and ureter. When a papilloma is seen protruding from the orifice of

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16. Sinkoe, S. J.; Fowler, M. F., and Berger, Louis: Wilms' Tumor of the Kidney: Report of Case with a Review of the Literature, *Am. J. Surg.* **25**:163 (July) 1934.

17. Shupe, T. P.: Tumors of the Renal Pelvis: Report of Two Cases, *Tr. Am. A. Genito-Urin. Surgeons* **27**:161, 1934.

the ureter, regardless of whether or not the bladder is involved, a diagnosis of renal and ureteral tumor is justified.

A simple papilloma, because of its habit of forming transplants in the ureter and bladder, must be considered at all times as potentially malignant. The accepted operative procedure in these cases is nephrectomy and total ureterectomy. This is especially true if the diagnosis is established as a result of the presence of transplants in the bladder and ureter.

Helfer and Schor<sup>18</sup> said that pyelography is a highly valuable method for the diagnosis of palpable tumor of the kidney. In the diagnosis of tumor of the kidney, repeated use of the pyelogram is an important aid in verifying characteristic changes in the form of the renal pelvis and in the position of the ureters. A tumor of the kidney may at times run its course without clinical symptoms. Therefore, whenever a mass is found in either side of the abdomen, it is necessary to determine by pyelography whether or not it is a tumor of the kidney. In cases of immovable tumor of the abdomen without symptoms from the bladder, it is at times difficult to determine whether or not the kidney is involved in the tumor mass. In cases of movable tumor, one is able, by means of pyelography, to decide definitely that the kidney is or is not involved in the mass. In cases in which the differential diagnosis of a tumor in the lower part of the abdomen presents difficulties, roentgenography of the intestine after the injection of an opaque medium is of great value.

*Trauma.*—Redi<sup>19</sup> said that the medical profession is divided into three groups with reference to the type of treatment to be applied following trauma of the kidney: out-and-out interventionists, moderate interventionists and out-and-out abstentionists. This diversity of opinion is caused in part by an error of interpretation, that is, by uncertainty as to the exact significance of the symptoms. It is a fact that there is no exact relation between the extent of the anatomicopathologic lesions in a given case and the general condition of the patient, and that the symptoms do not always give the key to the anatomic lesions and their later course of evolution. In all cases of renal trauma, the ascending and descending pyelograms, combined with the findings of functional tests, in their ensemble, give a clear picture of the type and extent of the lesion. Pyelography is not dangerous in cases in which the kidney has been injured, if carried out with complete asepsis; Redi has never encountered any complications from its use. With all the modern means of examination, it is possible to diagnose with approximate certainty

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18. Helfer, P. I., and Schor, M. I.: Die Bedeutung der Pyelographie für die Differentialdiagnose der Bauchgeschwülste, *Ztschr. f. urol. Chir.* **39**:322, 1934.

19. Redi, R.: Les lésions traumatiques du rein et leur traitement, *J. d'uro.* **38**:231 (Sept.) 1934.

(1) whether a rupture is limited to the parenchyma of the kidney, (2) whether it includes the renal plexus, and (3) whether it involves the capsule as well as all the other parts of the organ.

Intervention does not necessarily mean nephrectomy. It may mean the reconstruction of the kidney. Severi recently undertook experiments with rabbits, in which he traumatized in all possible ways the kidney on one side, to demonstrate what functional value would remain after the animals had recovered. In these experiments, however, the capsule and the pedicle never were deliberately injured. The animals always survived the injury; the wounded kidney was replaced in its bed and sutured in the various planes. From fifteen to ninety days later, the kidney of the other side was removed. Function in the damaged kidney was always demonstrated from the earliest days after operation. The course of recovery could be divided into three states: (1) hemorrhagic infiltration, (2) signs of resorption and (3) evidence of cicatricial sclerosis.

An interesting and novel observation was that lesions of the renal parenchyma are most severe at the junction of the cortex and medulla; here, they appeared at first as lacunae filled with blood, and at a later time, as pseudocysts. A second interesting fact was that in the medullary portion of the kidney the lines of rupture all followed the direction of the straight tubules, and were in a great part the result of dissociation of these. Thus, the tubules themselves were left intact for the most part and none had suffered irreparable injury. Consequently, function was not interrupted even in the days immediately following the traumatism. These results encourage the surgeon to go ahead with his efforts to reconstruct the injured organ, and they indicate that even a severely traumatized kidney may be expected to hold its own and to regain full function. Five illustrations or cases are outlined which demonstrate the justification for a waiting course. On the basis of these, and as a result of the experiments referred to, it may, therefore, safely be said that, unless the pyelogram shows that the kidney has been completely destroyed, or that it has been detached from its pedicle, the indication exists for partial or multiple resection of the organ, after a preliminary partial decapsulation and resection of the margin of the wound. The use of tampons is not advised, as it may lead to fistulas, but the placing of a Mikulicz drain is imperative. Complications, such as infection, irreducible hematuria, hematonephrosis, true traumatic hydronephrosis, rupture of the peritoneum, infarct of the kidney or rupture of the pedicle, may necessitate nephrectomy in such cases. The surgeon should act quickly, according to the indications. This is also true in cases in which there is perforation of the peritoneum, crushing



which was employed in 50 cases, resulted in 50 deaths; drainage only, which was employed in 51 cases, resulted in 23 deaths; nephrectomy plus drainage, which was employed in 54 cases, resulted in 14 deaths.

When a grossly diseased kidney is the source of bleeding, nephrectomy should be carried out. In cases in which the hematoma is of extrarenal origin, the prognosis is poor unless a blood vessel can be caught and ligated. In the third group, those cases in which no cause can be found, the best results follow nephrectomy.

#### TESTIS

*Tumor.*—Herger and Thibaudeau<sup>22</sup> reported cases of tumor of the testis from the State Institute for the Study of Malignant Disease at Buffalo. Their records show 63 cases in which tumor of the testis was treated at the institute. Of these, 56 were studied histologically. Fifty-five of these tumors are classed with the teratomas, while the other shows the histologic picture of a fibrosarcoma. The entire group of teratoma of the testis shows the average age of incidence to be 33 years. Eighty per cent of the patients were between the ages of 20 and 40 years, while 95 per cent were between 20 and 50 years of age. They noted that cases in which the tumor occurred in the second and third decades presented a much more unfavorable prognosis than did those in which the tumor occurred in the fourth and fifth decades. Their records showed that of 24 patients who were admitted before or at the age of 30 years, only 2 survived for three years, while 11 of the 30 patients who were between 31 and 50 years of age are still living after a three year period. For purposes of their study, Herger and Thibaudeau divided the malignant teratomas of the testis into five groups. In the first, malignant teratoma with adult features, they have included the tumors presenting definite adult structures, cartilage, fat cells, adult squamous epithelium, smooth muscle fibers and so forth. Even the malignant portions of these teratomas have presented evidence of adult type and have revealed their source from more or less differentiated cells. The records of the institute show 7 instances of this type of tumor.

The second group, embryonal carcinoma (seminoma), are tumors made up of large, round or polyhedral cells which have vesicular hyperchromatic nuclei characteristically growing in large sheets or alveoli. Twenty of the tumors belonged in this histologic group. Only 1 of the patients who had tumors of this type presented himself without demonstrable metastasis; 1 is alive and well ten years after irradiation and orchidectomy; 2, who have undergone treatment for less than one

22. Herger, C. C., and Thibaudeau, A. A.: Teratoma of Testis, *Am. J. Cancer* 22:525 (Nov.) 1934.

year, have persistent metastasis; 1 has not been traced, and the other 15 are dead. Twelve of the deceased survived for less than one year; the remaining 3 lived fifteen months, two years, and four years and nine months, respectively. In this group, treatment usually caused some recession of the metastasis, but rarely was complete disappearance noted. Apparently, the treatment was effective only in producing a temporary restraint of growth of the tumor; increased activity or new metastasis ultimately appeared which did not respond to treatment.

In the third group, embryonal carcinoma with lymphoid stroma, the presence of lymphocytes in the stroma in varying numbers is characteristic. After histologic examination, 17 of the tumors were classified in this group. In these cases, the patients presented themselves for treatment at the institute. Of these, 9 did not reveal demonstrable metastasis, while 8 revealed definite metastasis or local recurrences. The 9 patients who did not reveal metastasis were all treated with roentgen rays of high voltage and orchidectomy, and in none of these cases have recurrences or metastasis developed. All of these patients are alive and well. Of the 8 patients who revealed metastasis at the time of their admission, 3 are dead after living for four years, two and one-half years, and ten months, respectively. The remaining 5 are alive and apparently well, 1 for ten years, 1 for three years, 1 for one year, and 2 recent patients, still undergoing treatment, for less than one year.

Embryonal adenocarcinoma, which comprises the fourth group, presents definite characteristics. The typical picture is that of alveoli which are lined with large cuboidal or low columnar cells with hyperchromatic nuclei. The growth is often papillary, though in some areas it may assume a more solid form, with smaller cells and less differentiation. Herger and Thibaudeau have studied 11 cases of this type of tumor of the testis. Metastasis or local recurrence was present in all the patients when first seen. Only 1 patient who had this type of tumor is still living. Treatment of this type of tumor was of no avail, and the patients, all but 1, succumbed in from two to eight months. In this particular group of tumors, the clinical course was uniformly and rapidly fatal.

Chorionepithelioma, which comprises the last group, is identical in histology with the same tumor in the uterus. Characteristically, it presents the usual syncytial cells, which often resemble squamous epithelial cells, some multinucleated, in more or less disorderly arrangement. In the majority of cases, the usual treatment of simple orchidectomy followed by irradiation of the lymph-bearing areas was carried out. Usually the patients were referred and had undergone operation elsewhere, before admission to the institute. Often several months had elapsed between operation and irradiation. It is most desirable that patients

with this type of tumor be referred for treatment immediately after operation, as otherwise valuable time is lost and opportunity is provided for a spread and increase in the amount of tumor tissue. Irradiation has consisted of high voltage roentgen rays (200 kilovolts) with an effective wavelength of 0.16 angstrom. For abdominal and thoracic areas, a total of approximately 2,500 roentgens, divided between two fields, anterior and posterior, is administered in a period of eight days. This is repeated in from six to eight weeks. Some patients have been treated with the 4 Gm. radium element pack. At from 10 to 15 cm. skin distance, erythema doses are applied to anterior and posterior fields. Both of these procedures apparently have resulted in complete regression of large mediastinal metastases. Large abdominal masses also vanish rapidly in some cases. Of 36 patients available for three year statistics, 13 (36 per cent) survived three years or longer. Of 21 patients available for five year statistics, 7 (33.3 per cent) survived five years or longer. The authors stated that their limited experience with the quantitative Aschheim-Zondek reaction convinces them of its value as a diagnostic procedure and as an aid in the conduct of treatment.

Hinman and Powell<sup>23</sup> expressed the opinion that the pituitary body, pregnancy and embryonal tumors are known causes of the appearance in the urine of gonad-stimulating hormones. The stimulation of the growth of the gonads and genitals of infantile animals varies with the origin of the hormone producing it, the amount present in the urine and the animal used for the injections. The microscopic ripening of graafian follicles is more easily studied with mice than with rats. The gross enlargement of the uterine horns is more definite in rats than in mice. At the age of 20 or 21 days the ovary of the rat normally may show open follicles. The hydrocele fluid in the presence of tumor of the testis contains more of the hormone than does the urine of the patient.

The majority of tumors of the testis are embryonal, and the urine of patients who have these tumors contains a substance which produces gross enlargement of the uterine horns or microscopic ripening of the ovarian follicles when injected into infantile female mice and rats. The presence of such a gonadotropic hormone in the urine of a patient who has a tumor of the testis is presumptive evidence of malignancy of the tumor, and its absence is strong, but not definite, evidence against malignancy. The effect of irradiation on the amount of hormone in the urine, as determined by quantitative methods before and after the

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23. Hinman, Frank, and Powell, T. O.: The Gonadotropic Hormone in the Urine of Men with Tumor of the Testis, *Tr. Am. A. Genito-Urin. Surgeons* 27: 359, 1934.

irradiation, gives a good indication of the radiosensitivity of the tumor and may be used as a therapeutic test, in conjunction with the clinical effect on metastasis, when present. The effect of irradiation as a therapeutic test must be interpreted in conjunction with the histologic structure of the tumor, the clinical absence of metastasis, or the character of the metastasis when present, and the physical condition of the patient. The hormonal test permits a more accurate prognosis and a better control of therapy than has been possible heretofore, and may be of value in the classification of tumors the nature of which is in doubt from histologic study alone.

Hinman<sup>24</sup> said that the first step in the treatment of tumors of the testis is early and definite diagnosis. The hormonal test seems to indicate with accuracy the presence or absence of a malignant growth of the testis, but it is not entirely specific. A positive result may be caused by the pituitary hormone, which is increased because of gonadal deficiency, such as occurs with bilateral castration, or cyclically among normal men; it also may be caused by an embryonal tumor elsewhere than in the testis. A negative result is good, though not positive, evidence that there is not a malignant tumor of the testis. A pure seminoma may not cause the excretion of the hormone. The diagnosis can be determined definitely by histologic examination after castration. A study of histologic structure is necessary to prognosis and the control of treatment. Until recently, all tumors of the testis were regarded clinically as similar, always malignant, and as having the same route of metastasis. Experience with radiation has demonstrated a marked variability in the sensitivity of these various growths, and the newly applied hormonal test shows a difference in the amount of hormone excreted in the urine of patients who have different types of malignant tumors.

The second step in the treatment of tumors of the testis is the determination of whether or not there is metastasis by clinical examination and the biologic test. Patients who have no metastasis fail to excrete the hormone within two weeks after castration. When the hormone persists, though reduced in quantity, metastasis is probably present, even though it cannot be demonstrated clinically.

The third consideration in the treatment of a tumor of the testis is radiosensitivity. This can be predicted by past experience with similar tumors and can be tested clinically by noting the effect of irradiation on metastasis when present and on the amount of hormone in the urine. The determination of this sensitivity may be called the therapeutic test of irradiation.

24. Hinman, Frank: The Prognosis and Treatment of Tumors of the Testis, *Tr. Am. A. Genito-Urin. Surgeons* 27:379, 1934.

On the basis of diagnosis, metastasis and radiosensitivity, patients may be divided, for purposes of treatment and prognosis, into two groups: Group 1 includes those patients without clinical evidence of metastasis who are in good physical condition; these can be subdivided by the result of a hormonal test, two weeks after castration, into a negative subgroup and a positive subgroup. Group 2 contains patients who have clinical evidence of metastasis. Castration may be indicated for local relief, but mainly for diagnosis. Experience has demonstrated that these patients have tumors which are inoperable, and that irradiation is the only curative treatment. The prognosis depends on the extent and rapidity of growth of the metastases and on the general physical condition of the patient as well as on the type of tumor and its radiosensitivity.

Of 25 patients in group 1, 14 were subjected to radical operation, 9 for a tumor on the right side, and 5 for a tumor on the left side. Ten of these patients are living, all with a favorable prognosis. Four are dead. Seven disclosed metastases in the lymph nodes which were removed at operation. Four of these are living fourteen years, four years and ten months, one year and one month, and three months, respectively, after the operation. Three are dead. Seven had lymph nodes which did not show metastases when they were removed. In 2 of these cases, there was an unusual degree of endothelial hyperplasia; in one of the latter cases the patient is living and well six years and one month later, and in the other case the patient is dead. The 5 others are now living eight years and nine months, two years and eight months, one year and four months, one year, and one year, respectively, after the operation. Of the 11 patients who did not reveal metastases and who were treated by castration and roentgenotherapy, 8 are living; 1 for two years, with a favorable prognosis; 4 with only a fair prognosis because the hormonal tests are positive, and 3 with a definitely poor prognosis. Of the 4 patients with a fair prognosis, 1 lived seven years before metastasis occurred, but the amount of the hormone in the urine is increasing in spite of roentgenotherapy; 1 has lived seven years since castration, and, although metastasis is not evident clinically, the amount of the hormone in the urine is increasing. The other 2 who have a fair prognosis have lived one and three years, respectively, without clinical evidence of a metastasis, but with positive hormonal tests.

Of the 29 patients in group 2, only 10 are alive; 4 have a fair prognosis and are living five years, one and one-half years, six months, and a few months, respectively, after the operation, but all have positive hormonal tests, and 6 have a poor prognosis (radioresistant).

MacKenzie<sup>25</sup> reported 2 cases of malignant growth in the undescended testis, but expressed the opinion that there is not much danger of malignant changes in undescended testes, whether inguinal or abdominal. There is no definite proof that undescended testes are predisposed to malignant changes. In a review of the literature, various reports contain assertions to the effect that tumors occur from thirty to three hundred times as frequently in the undescended as in the normally placed gonad. There also are differences of opinion regarding the relative frequency of malignant conditions in testes which are situated in the inguinal region or in the abdominal cavity. The following are some of the reports regarding malignant growths in undescended testes: Deane reported that 13.5 per cent of all tumors of the testis were found in undescended organs. Hinman reviewed 649 cases of carcinoma of the gonads and found that 12.2 per cent involved undescended testes. Rubaschow reviewed the cases of this condition which had been reported by 21 observers, and found that in 11 per cent of the whole group tumors were present. This figure is a rather high one. Eccles reported 859 cases of undescended testes without finding a malignant growth in any of them. Coley did not find a malignant tumor in 1,357 cases of undescended testes. Kocher found only 1 malignant tumor in 1,000 cases. Hinman expressed the opinion that 1 instance of malignant tumor of an abdominal testis is found in every 60,000 cases of undescended testes.

MacKenzie's method of treatment of tumor of the testis, whether undescended or normally placed, has been changed in the past few years. A course of treatment with roentgen rays of high voltage is first given. This is followed by orchidectomy and several courses of roentgenotherapy extending over a long period. Patients report every two or three months for observation. Since this new method has been used, the results have been more satisfactory; even those patients who disclosed metastases when they first sought treatment seem to have improved. In a small number of cases in which there were metastases in the thorax and retroperitoneal glands, the masses have entirely disappeared or have been reduced considerably in size after the course of treatment with roentgen rays of high voltage. MacKenzie expressed the opinion that no undescended testis per se should be subjected to orchidectomy.

Robertson and Gilbert<sup>26</sup> summarized 7 cases of tuberculosis and carcinoma of the testis from the literature and reported a case of their

25. MacKenzie, D. W.: Malignant Growths in the Undescended Testis: Review of the Literature and Report of Two Cases, *Tr. Am. A. Genito-Urin. Surgeons* 27:399, 1934.

26. Robertson, J. P., and Gilbert, J. B.: Coexistent Cancer and Tuberculosis of the Testicle: Case Report and Complete Review of the Literature, *J. Urol.* 32:291 (Sept.) 1934.

own. The youngest patient was 28 years of age, while the oldest was 53 years of age; the average age of these patients was 38.3 years. The right side was involved in 4 cases, the left in 3 cases, and in one instance an undescended testis on the right side was involved. The duration of the known presence of a tumor varied from six weeks to four years. In 3 instances, tuberculosis was present elsewhere in the body: in the bones (rib) in 1 case, and in the lungs in 2 cases. Three patients previously had had gonorrhea. Carcinoma was associated with the tuberculosis in 6 instances, and seminoma was associated with the tuberculosis in 2. A survey of the coincidence of tuberculosis of the epididymis and malignant tumors of the testis is recorded, as well as the incidence of tumors of the testis which were associated with pulmonary tuberculosis. It is emphasized that diagnosis in the atypical case often is difficult; mistakes are costly, and surgical exploration or irradiation should be employed in cases in which the nature of the tumor is in doubt. The routine use of the quantitative Aschheim-Zondek reaction is advocated.

*Castration.*—McCullagh and Renshaw<sup>27</sup> subjected 12 postpubertal castrates to careful clinical and laboratory studies to increase familiarity with the diagnostic evidence of hypogonadism of man. Complete castration produced nervous and vasomotor disorders as early as the third day after operation. This nervous excitability was in some cases associated with a tendency to psychoneurosis, emotional instability and restlessness—a sensation not unlike that resulting from a mild overdose of thyroid extract. Hot flashes occurred as many as four or five times daily for a period of several years, and tended gradually to decrease in number and severity. All of the patients had diminished sexual potency and libido. Sexual impotence was not a distressing symptom in the absence of sexual desire, but in 3 cases in which there was a partial retention of libido even partial impotence became a distressing symptom. After the acute nervousness had subsided, the patients tended to display a quiet, phlegmatic temperament. Atrophy of the prostate was a constant and striking feature in all of these cases. The size of the prostate glands varied from a half to a fifth of normal. Vigorous and repeated massage failed to produce any prostatic secretion in 8 of the cases. Atrophy of the penis was recorded in only 5 cases. Hirsuties was definitely reduced, except for the scalp, and was of a female distribution. Eight patients showed abnormal accumulations of fat, chiefly about the abdomen and breasts. There were no gross skeletal changes. The skin became somewhat atrophic and was thin, slightly dry and finely wrinkled in 11 cases. The teeth, finger-nails, thyroid gland and pituitary body did not reveal any changes. Eight of 9 patients who were subjected to

27. McCullagh, E. P., and Renshaw, J. F.: Effects of Castration in the Adult Male, *J. A. M. A.* 103:1140 (Oct. 13) 1934.

the Friedman test revealed definite evidence of increased gonad-stimulating principle in the urine, as compared to normal men subjected to similar tests. The basal metabolism of these patients was low. Serum calcium estimations were within normal limits in 11 cases.

The testis hormone, which is prepared from urine, when available for adequate dosage, produced considerable improvement in the subjective symptoms of hypogonadism. It is too early to evaluate accurately the benefits of this type of treatment.

#### EPIDIDYMISS

*Filariasis.*—Ferrer <sup>28</sup> said that filariasis of the spermatic cord and filariasis of the epididymis are two different lesions, with separate symptoms. A correct diagnosis of either condition can be made with a definite degree of certainty before determining the operative procedure to be used. Microfilariae may persist in the superficial circulation for a number of years even after radical surgical intervention, provided that a secondary infection with adult organisms has taken place later, or that there is another focus producing the periodic outpouring of microfilariae.

The principal differences between filariasis of the spermatic cord and that of the epididymis are as follows: In filariasis of the cord there is a history of intermittent hydroceles with a final permanent hydrocele. This condition is characterized by fibrosis, anterior nodules and typical sequelae of inflammatory reaction of the anterior portion of the cord. The diagnosis is confirmed by the finding of the living or dead parasite. In filariasis of the epididymis, there are attacks of colic, with constitutional symptoms, and there never is a hydrocele during or after the attack, unless it may be caused by other factors. The involvement is circumscribed to the globus major, and the adult organism should be found in sections of the specimens which are removed to confirm the preoperative diagnosis. Only radical surgical intervention will cure the disease. It should be remembered, however, that the condition may be bilateral, and that the testis should be preserved intact for internal, and possibly for external, secretory function.

#### SPERMATIC CORD

*Tumors.*—Fresnais and Mouchet <sup>29</sup> reported a case of malignant tumor of the spermatic cord, which recently was observed in Marion's clinic. The growth, which began 1 cm. above the testis and measured

28. Ferrer, J. C.: Filariasis of the Spermatic Cord and of the Epididymis, *J. Urol.* **32**:710 (Dec.) 1934.

29. Fresnais, Jean, and Mouchet, Alain: Un cas de tumeur maligne du cordon spermatique, *J. d'uro.* **38**:259 (Sept.) 1934.



11 cm. in length, involved almost all the elements of the spermatic cord, which could not be recognized or dissociated; the vas, however, remained intact, and the testis, epididymis and tunica vaginalis were all normal. The exact nature of the tumor could not be determined, but in view of the polymorphism of its cells and the presence of numerous eosinophils, a diagnosis of lymphogranulomatosis appears to deserve consideration, although epithelioma and sarcoma could not be excluded. A search of the literature revealed only 44 cases of malignant tumor of the spermatic cord, 22 of which were analyzed by Patel and Chaliar in 1909, while the other 22 have been reported by various authors since that time. In 38 of the cases, the tumors were sarcomas, and among these the fibroblastic sarcomas were the most characteristic. Sarcomas of the spermatic cord, however, rarely present a uniform appearance. Celso and Karo were both struck by the variety of the cellular elements in the tumor which was found in their case, and decided to call it by the inexact name of "poly-morphous-celled sarcoma, myxo-lipo-sarcoma, and myxo-chondro-sarcoma." The most individualized group is that of lymphosarcoma, the round cell sarcoma of the older authors, which is characterized by autonomous and undifferentiated proliferation of the lymphoid cells, but the only clearcut case of this type of tumor was that reported by Allende and Gonzalez<sup>30</sup> in 1930. All types of sarcoma may affect the spermatic cord, and the tumor most frequently is one of the mixed type.<sup>31</sup> The conspicuousness of certain tissues, for example, the lipid tissue, seems to point to a tumor which originally was benign but which has undergone malignant degeneration. However, the line between epithelioma and sarcoma is not easy to draw, and the case reported here is particularly open to this indefiniteness. No satisfactory classification of tumors of the spermatic cord has ever been made. The tumors generally appear between the ages of 40 and 70 years. The site of the tumor usually is on the left side of the cord; it may be in either the inguinal or the scrotal portion of the cord. The growth develops insidiously; its evolution may require years or only months. The prognosis should be reserved. In the case reported, the tumor has not reappeared in the five months that have elapsed since its removal. Treatment consists in the extirpation of the tumor and the testicle en bloc after high ligation of the cord; such extirpation is generally easy, owing to the absence of adhesions. Postoperative radiotherapy is indicated.

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30. Allende, J. M., and Gonzalez, R.: Tumor del cordón espermático, Bol. y trab. de la Soc. de cir. de Buenos Aires **14**:671 (Oct. 1) 1930.

31. Hinman, Frank, and Gibson, T. E.: Tumors of the Epididymis, Spermatic Cord and Testicular Tunics, Arch. Surg. **8**:100 (Jan.) 1924.

*Varicocele*.—Do Amaral<sup>32</sup> discussed the merits of a new method of surgical treatment of varicocele. After making the usual type of incision, as for inguinal hernia, the testis is exteriorized by making gentle traction on the cord, with the help of compression from below upward. Working from above downward, the vas deferens must be separated from the varicose veins by means of a grooved sound; at the lowermost part of the spermatic cord, this procedure can be done best with the aid of gauze compresses. The bundles of veins are separated from the vas, down to the testis. Then comes the most delicate part of the operation; this consists in the exposure and isolation of the varicose veins without rupturing any of the anastomoses. This is done from above downward, beginning at the uppermost part of the spermatic cord, where, instead of a confused agglomeration of innumerable interlacing veins, only two or three relatively large vessels are found, which constitute the termination of all the bundles of the pampiniform plexus. The tunica vaginalis is now open and inverted, and is held in place by two or three catgut stitches, no. 00, as in the treatment of hydrocele, but the stitches are so placed as to form a jacket over that part of the spermatic cord which remains outside of and below the aponeurosis of the external oblique muscle, to prevent venous stasis. The vas, with its artery and satellite veins, is then separated and placed under the internal oblique and transversalis muscles, which in their turn are sutured to Poupart's ligament with chromicized catgut or with silk; the testis is replaced in the scrotum, care being taken not to make any torsion of the cord. At this point comes the deviation from the usual procedure. Instead of extirpating the varicose veins, they are left lying extended over the internal oblique and transversalis muscles, and covered with the aponeurosis of the external oblique muscle, which hides and compresses them, as an elastic stocking does the veins of a leg. It was believed that the veins would be held in this position, owing to the adhesions which would form later. But when the method did not prove effective in this respect, the device of a small buttonhole in the aponeurosis of the external oblique was tried, and served very satisfactorily; the varicose veins were hooked out through this small opening in the form of a loop, by means of a retractor, after which a U-shaped stitch was placed in the middle of the buttonhole to prevent the veins from slipping down again into the scrotum. In restoring the external orifice of the inguinal canal, care must be taken to narrow it, leaving barely enough room for the spermatic cord to pass from the deep plane to the veins of the supra-aponeurotic plane. The results obtained with this buttonhole modification were highly satisfactory; all the objective and subjective

32. do Amaral, Zephirido: Traitement du varicocèle par une nouvelle méthode chirurgicale, J. d'urolog. 38:249 (Sept.) 1934.

symptoms disappeared, the integrity of the vessels, both arteries and veins, was conserved, reflux was corrected, and the bulging varicosities within the scrotum, which are so distracting to the patient's mind, disappeared. The procedure corrects orchidoptosis, and also can be used to correct a hernia or a hydrocele at the same time as the varicocele is corrected.

*(To be concluded)*

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### CORRECTION

In the article by Drs. L. J. Adelstein and George H. Patterson, entitled, "Surgical Treatment of Ependymal Glioma of the Spinal Cord," in the June issue (*Arch Surg.* **30**:997, 1935), figures 2 (page 1004) and 6 (page 1009), but not the legends, have been transposed.

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## SLIPPING OF THE CAPITAL EPIPHYSIS OF THE FEMUR IN ADOLESCENCE

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NEW YORK

The cause of slipping of the capital epiphysis of the femur in adolescence is still disputed. Renal rickets, osteomalacia, late rickets, trauma and other causes have been cited.<sup>1</sup> For this reason it was deemed worth while to report three cases in which during operative correction

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1. Whitman, R.: Observations on Bending of the Neck of the Femur in Adolescence, New York M. J. **59**:769 (June 23) 1894. Sudeck, P.: Zur Anatomie und Aetiologie der Coxa Vara Adolescentium, Arch. f. klin. Chir. **59**:504, 1899. Blum, V.: Die Coxa Vara als Belastungsdeformität, *ibid.* **69**:1065, 1903. Froelich: Beitrag zur Aetiologie der nichtsymptomatischen Coxa Vara, Ztschr. f. orthop. Chir. **12**:80, 1903. Joachimsthal: Die Aetiologie der Schenkelhalsverbiegungen, *ibid.* **12**:52, 1903. Fittig, O.: Die Epiphysenlösung des Schenkelhalses und Ihre Folgen, Arch. f. klin. Chir. **89**:912, 1909. Elmslie, R. C.: Coxa Vara: Its Pathology and Treatment, London, H. Frowde, 1913. Steindler, A.: Coxa Vara Adolescentium Traumatica, J. A. M. A. **64**:216 (Jan. 16) 1915. Kirmisson, E.: La coxa vara traumatique, Rev. d'orthop. **24**:89, 1913; **26**:240, 1918. Fromme, A.: Die Spätrachitis und ihre Beziehungen zu chirurgischen Erkrankungen, Beitr. z. klin. Chir. **118**:493, 1920. Platt, H.: Pseudo-Coxalgia, Brit. J. Surg. **9**:366 (Jan.) 1922. Wilson, P. D.: Displacement of Upper Epiphysis of Femur Treated by Open Reduction, J. A. M. A. **83**:1749 (Nov. 29) 1924. Key, J. A.: Epiphyseal Coxa Vara or Displacement of the Capital Epiphysis of the Femur in Adolescence, J. Bone & Joint Surg. **8**:53 (Jan.) 1926. Irwin, S. T.: Separation of the Upper Epiphysis of the Femur, Irish J. M. Sc. **1**:71 (Feb.) 1929. Huc, G.: La coxa vara de l'adolescence, Rev. d'orthop. **17**:397 (Sept.) 1930. Klein, N.: Ueber Ossifikationsstörungen beider Hüftgelenke auf endokriner Grundlage, Röntgenpraxis **3**:550 (June) 1931. Taylor, V. J. M.: Displacement of the Upper Femoral Epiphysis, Brit. M. J. **2**:1003 (Dec. 3) 1932. Capener, N.: Two Cases of Adolescent Coxa Vara, Proc. Roy. Soc. Med. **25**:1077 (Jan.) 1932. Eikenbary, C. F., and Le Cocq, J. F.: Separation of the Upper Femoral Epiphysis, West. J. Surg. **40**:432 (Aug.) 1932. Kienbock, R.: Ueber juvenile Schenkelhals-Malazie hypophysären Ursprungs, Ztschr. f. orthop. Chir. **57**:408 (Oct.) 1932. Brailsford, J. F.: Slipping of Epiphysis of Head of Femur: Its Relation to Renal Rickets, Lancet **1**:16 (Jan. 7) 1933. Fischl, E.: Beobachtungen über die Osteochondritis Deformans Coxae Juvenilis, zugleich ein Beitrag zur Pathogenese der Epiphysenlösung am coxalen Femurende, Arch. f. orthop. u. Unfall-Chir. **33**:456, 1933. Bade, A.: Zur Abgrenzung der verschiedenen Formen von Coxa Vara, Ztschr. f. orthop. Chir. **59**:53, 1933. Wardle, E. N.: Etiology and Treatment of Slipped Epiphysis of the Head of the Femur, Brit. J. Surg. **21**:313 (Oct.) 1933.

sufficient bone was removed for pathologic examination.<sup>2</sup> Particular attention was paid to the epiphyseal cartilage plates and to the head and neck of the femur.

#### REPORT OF CASES

CASE 1.—A girl 11 years of age complained of severe pain in the region of the right hip for two days prior to admission. Physical examination showed her to be well developed. The right hip joint was in a position of 125 degrees at the angle of greatest extension and in 15 degrees of adduction. Owing to severe pain and spasm clinical examination of the right hip joint could not be done adequately. It was possible to flex the left hip to 90 degrees and to extend it completely. There was, however, but 10 degrees of passive abduction and 25 degrees of passive adduction.

Roentgenograms of the region of the right hip disclosed slipping of the capital epiphysis of the femur (fig. 1 *A*). Roentgenograms of the left hip showed widening of the neck of the femur with compression of the capital epiphysis (fig. 1 *B*). Thus, in addition to the lesion on the right side there existed a healed slipped capital epiphysis on the left.

The condition on the right side (recently slipped epiphysis) was corrected by closed manipulation.<sup>3</sup> A few weeks later, arthroplasty for reconstruction of the

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2. Müller, E.: Ueber die Verbiegung des Schenkelhalses im Wachstumsalter, *Beitr. z. klin. Chir.* **4**:137, 1888. Hofmeister, F.: Coxa Vara, eine typische Form der Schenkelhalsverbiegung, *ibid.* **12**:244, 1894. Kocher, T.: Ueber Coxa Vara, *Deutsche Ztschr. f. Chir.* **38**:521, 1894; **40**:411, 1895. Maydl, K.: Coxa Vara und Arthritis Deformans Coxae, *Wien. klin. Rundschau* **11**:153, 1897. Sprengel, P.: Ueber die traumatische Lösung der Kopfepiphyse des Femur und ihr Verhältnis zur Coxa Vara, *Arch. f. klin. Chir.* **57**:805, 1898. Alsberg, A.: Anatomische und klinische Betrachtungen über Coxa Vara, *Ztschr. f. orthop. Chir.* **6**:106, 1898. Haedke, M.: Zur Aetiologie der Coxa Vara, *Deutsche Ztschr. f. Chir.* **66**:89, 1902. Schlesinger, A.: Zur Aetiologie und pathologischen Anatomie der Coxa Vara, *Arch. f. klin. Chir.* **75**:629, 1905. Helbing, C.: Die Coxa Vara, *Ztschr. f. orthop. Chir.* **15**:502, 1906. Grashey, R.: Coxa Vara Retroflexa Traumatica, *Beitr. z. klin. Chir.* **70**:186, 1910. Frangenheim, P.: Weitere Untersuchungen über die Pathologie der Coxa Vara Adolescentium, *ibid.* **72**:239, 1911. Kappis, M.: Klinische und Röntgenologische Dauerergebnisse der Epiphysenlösung am Oberschenkelhals, *Zentralbl. f. Chir.* **51**:113 (Jan. 19), 1924. Ferguson, A. B., and Howorth, A. B.: Slipping of the Upper Femoral Epiphysis, *J. A. M. A.* **97**:1867 (Dec. 19) 1931. Camitz, H.: Étude comparée sur la coxa vara dite congénitale et l'osteochondrite coxale juvénile (coxa plana), *Acta chir. Scandinav.* **73**:521, 1934. Waldenström, C. H.: Necrosis of the Femoral Epiphysis Owing to Insufficient Nutrition from the Ligamentum Teres: A Clinical Study Mainly Based on Experiences with the Treatment of Epiphysiolysis Capitis Femoris, *ibid.* **75**:185, 1934.

3. Jahss, S. A.: Displacement of the Upper Epiphysis of the Femur (Adolescent Coxa Vara) Treated by Closed Reduction, *J. Bone & Joint Surg.* **29**:856 (Oct.) 1931. Perkins, G.: The Treatment of Adolescent Coxa Vara, *Brit. Med. J.* **1**:55 (Jan. 9) 1932. Pomeranz, M. M., and Sloane, M. F.: Slipping of the Proximal Femoral Epiphysis: Therapeutic Results in One Hundred and One Cases, *Arch. Surg.*, **30**:607 (April) 1935.

left hip joint was performed.<sup>4</sup> The bone that was extirpated came to the laboratory in three separate pieces. These were covered by rather smooth, dull articular cartilage. In addition, a fragment of synovial membrane was received which disclosed nothing abnormal on macroscopic or microscopic examination.

On reconstructing the three fragments of bone it was found that they represented most of the capital epiphysis of the femur. This had become flattened and as a result of the mushrooming had extended considerably over the neck, particularly toward the greater trochanter. On gross serial section the epiphysis was seen to bear evidence of being moderately sclerosed, especially beneath the covering cartilage of the portion which fitted into the acetabulum. Toward the greater trochanter the flattened epiphysis was somewhat atrophic. The moderately irregular epiphyseal cartilage plate showed interruptions like those observed in plates which close normally. A few small islets of cartilage-like tissue, apparently connected with the plate, were observed extending into the epiphysis. A portion of the neck of the femur came with the specimen; this was entirely encircled by the epiphysis as by a cuff.

After reorientation of the fragments of bone, seven sections were prepared for histologic examination: section 1 was closest to the acetabulum, and section 7 was nearest the greater trochanter (fig. 1 C). The pathologic diagnosis based on macroscopic examination was spontaneously healed or healing slipped capital epiphysis.

Microscopic examination of section 1 revealed compressed epiphyseal tissue. The gliding surface of the cartilage was slightly irregular in certain areas. The trabeculae beneath the cartilage showed nothing unusual. The intertrabecular spaces contained both lymphoid and fatty marrow. The widened, abnormal epiphyseal cartilage plate presented a narrow layer of hypertrophic cartilage cells as well as a thin zone of provisional calcification. The epiphyseal plate showed areas of fibrosis and fibrocartilage. No necrosis of the trabeculae of the epiphysis was seen.

Section 2 disclosed slight roughening of the surface of the articular cartilage. The trabeculae of the capital epiphysis revealed nothing unusual. The head of the femur, however, had been compressed toward the epiphyseal plate. The latter presented an irregular zone of provisional calcification. In some portions of the plate large spaces were filled with blood pigment (fig. 2 A). Some of the cartilage of the epiphyseal plate near the pigmented zones had become fibrous.

Section 3 showed the articular cartilage within normal limits. The insertion of the ligamentum teres into the articular cartilage and bone marrow showed nothing unusual except stasis in the capillaries in the subchondral fibrous tissues. The trabeculae of the epiphysis were thickened in some areas without showing evidence of necrosis. The intertrabecular spaces in the epiphysis contained fatty marrow for the most part. The epiphyseal plate was irregular in contour as well as in thickness. In the area marked *a* in figure 1 C the plate had buckled or bent on itself so that the proliferating zones were facing each other (fig. 2 B and C). Small localized areas of degeneration in the form of long slits as well as cysts in the epiphyseal plate were seen. The endochondral ossification was not disturbed to any great extent (fig. 2 D). The neck of the femur was covered on its inferior surface by articular cartilage. The trabeculae of the neck were thin and numerous, with no signs of necrosis. The marrow was lymphoid.

4. Kleinberg, S.: Reconstruction: Arthroplasty Operation for Hip, *Am. J. Surg.* 18:64 (Oct.) 1932.

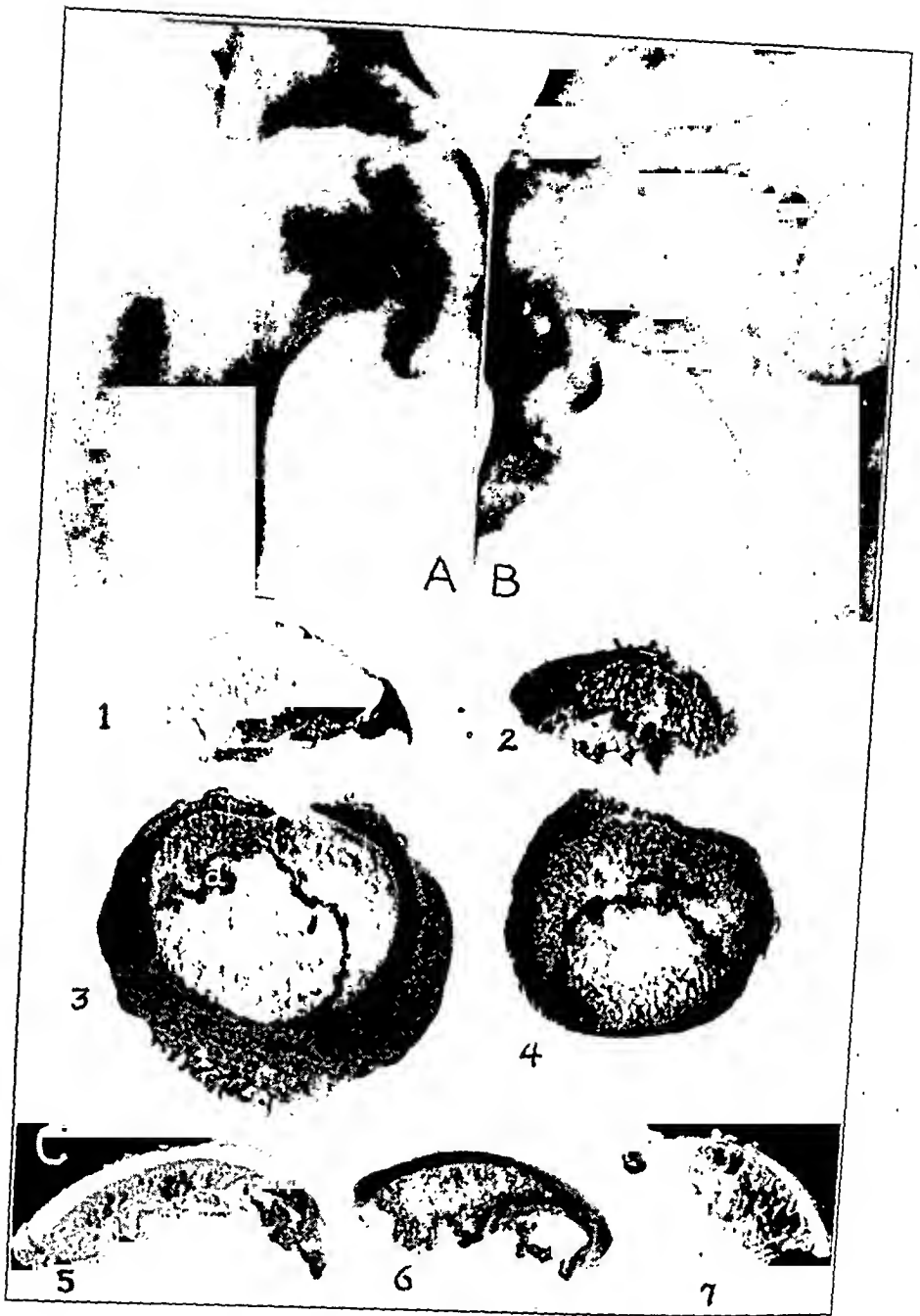


Figure 1

Fig. 1 (case 1).—*A*, slipping of capital epiphysis of right femur; *B*, compression of slipped epiphysis against neck of left femur. *C*, sections from head and neck of left femur. The first section was closest to the acetabulum, and the seventh was nearest the greater trochanter. Area  $\alpha$  shows buckling in the cartilage plate.

Fig. 2 (case 1).—Sections of original upper epiphyseal cartilage plate. In *A* are cysts, cracks and fibrosis. Considerable blood pigment is seen in cartilaginous defects. Zone of provisional calcification shows herniation into metaphysis. An island of original epiphyseal plate is seen in metaphysis;  $\times 60$ . In *B* are numerous small cysts and cracks, as well as buckling (*Y*) in epiphyseal plate;  $\times 30$ . *C* is an enlargement of area *Y* in figure 2*B*;  $\times 125$ . Note that proliferating zones face each other. In *D* is a long linear crack in proliferative zone. Endochondral ossification has not been disturbed;  $\times 75$ .

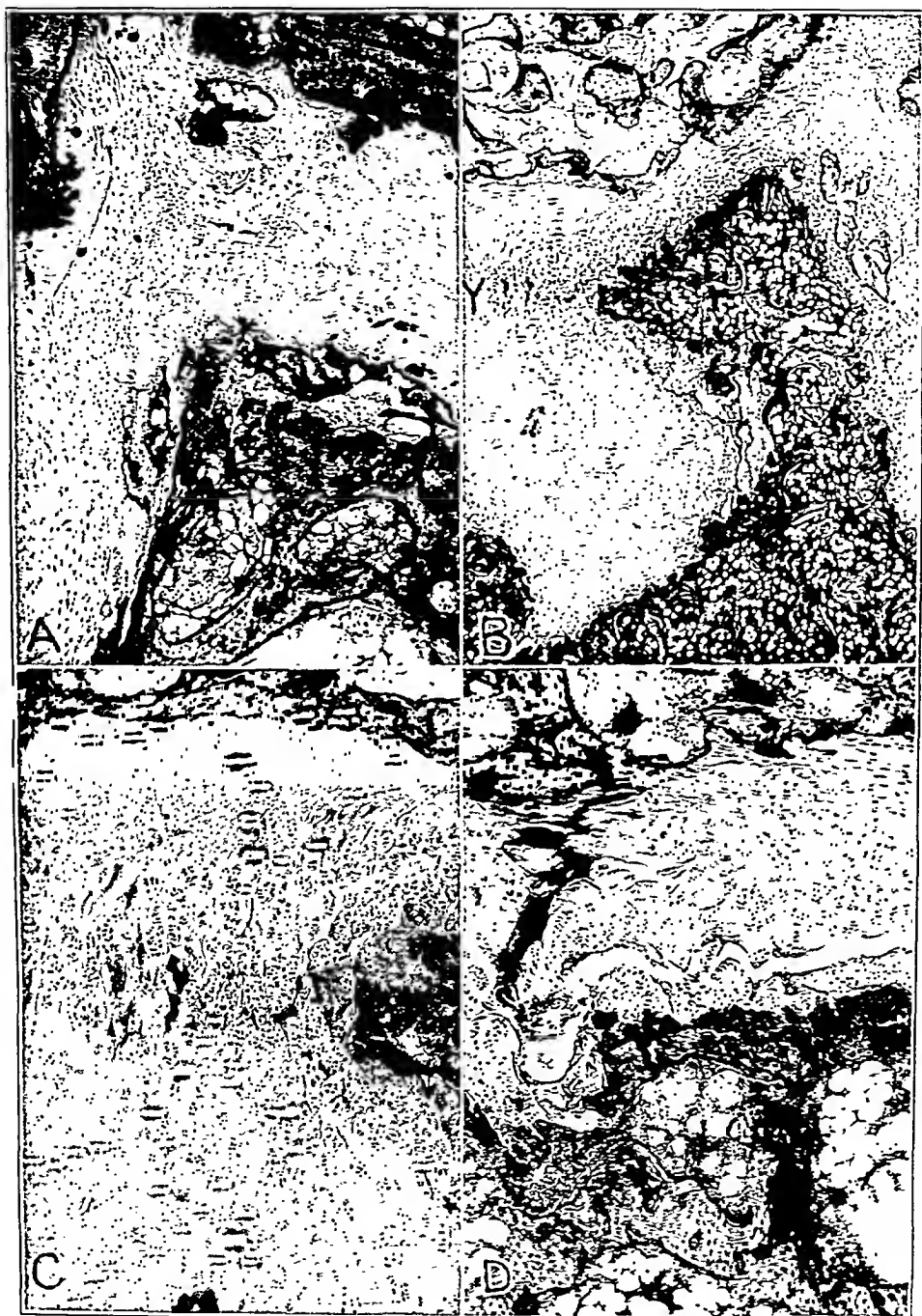


Figure 2





Figure 3

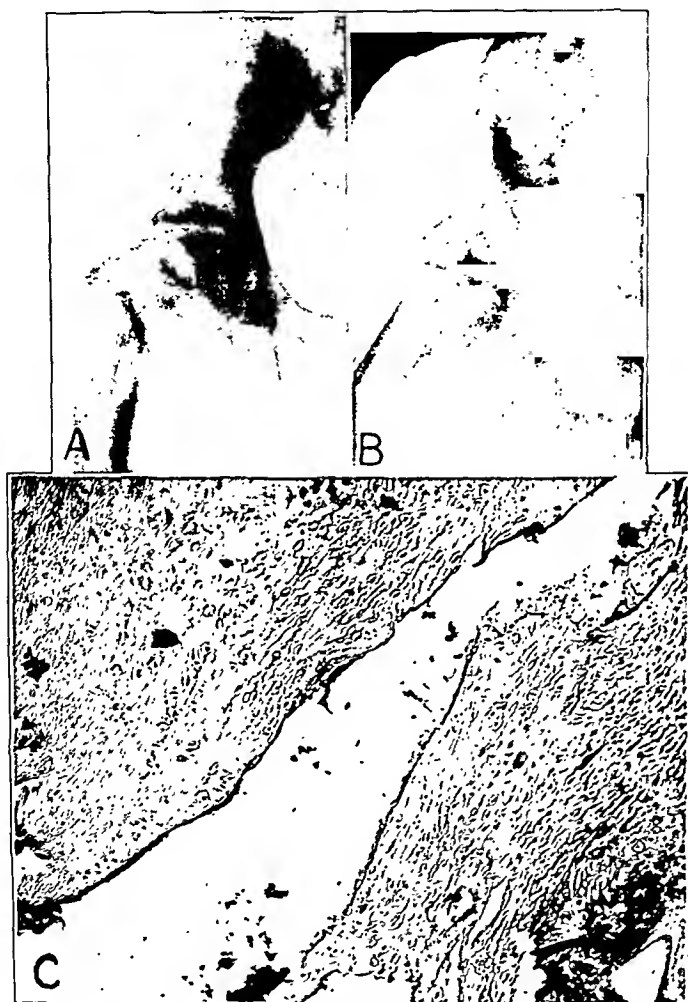


Figure 4

Fig. 3 (case 1).—*A*, islands of displaced original upper epiphyseal cartilage plate in capital epiphysis. Note degenerated areas in cartilage;  $\times 75$ . *B*, an enlargement of a portion of figure 3 *A* showing foreign body giant cells about degenerated areas of cartilage;  $\times 175$ . In *C*, a linear crack extends from zone of resting cartilage cells through trabeculae of femoral epiphysis;  $\times 75$ .

Fig. 4 (case 2).—*A*, downward and backward slipping of capital epiphysis and coxa vara of right femur. *B*, nonunion of osteotomized neck of femur (fig. 4 *A*) twelve weeks after operation. *C*, a fissure in upper epiphyseal cartilage plate ( $\times 60$ ).

Section 4 revealed that except for some superficial roughening near the insertion of the ligamentum teres the articular cartilage was within normal limits. The intertrabecular spaces of the epiphysis were fibrous where the ligamentum teres existed. The subchondral bone disclosed no necrosis. The epiphysis, which had been flattened to some degree, contained several misplaced areas of upper epiphyseal plate, some parts of which were undergoing endochondral ossification. Some of the displaced degenerated segments of the upper epiphyseal plate in the capital epiphysis were enveloped for the most part by cellular and fibrous tissue and by foreign body giant cells (figs. 3*A* and *B*). A similar fibrous reaction of the marrow was noted in the distal portion of the epiphysis contiguous to the zone of resting cartilage cells of the original upper epiphyseal plate.

The cartilage plate of the capital epiphysis was irregular in thickness. In certain places it had buckled into the depths of the metaphysis. Several linear cracks containing fibrin and blood were noted in the plate distal to the zone of resting cartilage cells. While small areas of degeneration were present close to the linear cracks, larger areas of degeneration were present in the zone of resting cartilage cells. In one of these cystic areas loose fragments of the epiphyseal plate were seen. An interesting lesion was a microfracture line extending from the zone of resting cartilage cells directly through several of the trabeculae of the capital epiphysis (fig. 3*C*). Considerable hemorrhage was present. In addition, a healing microfracture of the inferior cortex of the neck was present.

Section 5 disclosed thick trabeculae in the epiphysis. They were closely set and contained few small areas of anuclear bone. There was some fibrocellular reaction in the marrow, which was most marked at the junction between the articular cartilage and the upper epiphyseal plate. Sections 6 and 7 revealed nothing additional.

CASE 2.—A boy aged 17 had a limp for one year. Shortly prior to the onset of his illness he had been hit with a rolling-pin on the right leg. For three months afterward he had experienced pain in the region of the right hip while sitting. Physical examination revealed him to be well developed. He walked with a limp on the right side. The right leg was 1 inch (2.5 cm.) shorter than the left. The right leg was held at an angle of 60 degrees of external rotation. It was possible to rotate internally approximately 25 degrees from the position of marked external rotation. Passive flexion of the right hip joint was limited to 90 degrees. No passive abduction was present.

Roentgenograms of the right hip joint revealed downward slipping of the capital epiphysis and slight coxa vara of the femur (fig. 4*A*). The treatment consisted of an osteotomy through the neck of the right femur. There was non-union of the fragments after twelve weeks (fig. 4*B*). At this time the head and portions of the neck of the femur were removed.

The specimen received for study consisted of the capital epiphysis and parts of the neck of the right femur. The articular cartilage revealed nothing noteworthy. A section of the head and neck demonstrated wavy irregular and reduplicated epiphyseal cartilage plates. Dense bone was observed between the broken fragments of the original epiphyseal plate.

Microscopic examination revealed slight roughening of the femoral articular cartilage. The subchondral bone in the head of the femur disclosed a slight increase in the size of the cell lacunae. Osteoblastic activity about the trabeculae in the capital epiphysis was marked. Very little endochondral ossification was present in the localized widened segments of the epiphyseal plate. Other portions of the plate, which were narrow, were undergoing closure. In still other areas fibrinous and cystic degeneration of the plate was prominent. A definite longitudinal split was seen in the epiphyseal plate (fig. 4*C*).

The diagnosis was tear and degeneration of the epiphyseal plate (in spite of nonunion of the neck, no necrosis of the capital epiphysis was noted).

CASE 3.—A boy aged 12 complained of pain in the right knee which started two weeks prior to his admission to the hospital. Physical examination revealed him to be a tall, obese boy who walked with a marked limp on the right side. Moderate genu valgum was present on each side. The right femur was in slight external rotation; abduction and adduction of that extremity were not limited; internal rotation and hyperextension were limited slightly. A roentgenogram of the region of the right hip revealed slight downward slipping of the capital epiphysis (fig. 5*A*).

Open correction was performed. A segment of bone was removed from the proximal surface of the neck of the femur and from the concave aspect of the loose head. The gross specimen consisted of two segments. The first was composed of a large piece of spongy bone (neck) covered in places with small pieces of cartilage (epiphyseal plate). The second was made up of spongy bone (epiphysis) with underlying areas of epiphyseal plate.

Microscopic examination of the first segment of tissue revealed a tear and degeneration of the epiphyseal plate near the cortex of the neck. Considerable hemorrhage was present (fig. 5*B*). Some portions of the original epiphyseal plate exhibited signs of degeneration, fibrosis, calcification, ossification and marked vascularization of the hyaline cartilage. In other segments of the plate normal endochondral ossification was found. Islands of herniated original epiphyseal plate located in the metaphysis were encircled by degenerated cartilage and necrotic bone. Another histologic preparation revealed abnormal endochondral ossification in the original epiphyseal plate, i. e., endochondral ossification on the epiphyseal and metaphyseal surfaces of the original epiphyseal plate (fig. 5*C*). Examination of the metaphysis revealed edema and fibrosis of the stroma in the marrow spaces. Osteoblastic activity was marked about the trabeculae of bone in the metaphysis (fig. 5*D*). Microscopic sections of the second segment of bone showed changes in the epiphyseal plate and in the marrow spaces of the capital epiphysis similar to those noted in the first specimen (*a*). The diagnosis was tear and degeneration of the capital epiphyseal plate of the femur with healing.

#### COMMENT

Histologic study of these specimens revealed no evidence of rickets, osteomalacia or specific osteitis fibrosa. The pathologic condition may be interpreted as a fracture through the upper capital epiphyseal plate of the femur and through some of the contiguous osseous trabeculae.

One cannot prove definitely that such a fracture was conditioned on a primary disease of the cartilage plate. Microscopic examination revealed that for the most part the upper epiphyseal plate showed only scattered foci of degeneration, usually close to tears or fractures of the epiphyseal cartilage plate. In these cracks blood pigment was usually present. The buckling of the plate plus the presence of herniated segments of the epiphyseal plate either into the epiphysis or into the metaphysis would tend to support the suspicion that trauma caused many of the microscopic observations. Many of the changes of the original epiphyseal plate, such as fibrosis, calcification and premature



Figure 5



Figure 6

Fig. 5 (case 3).—*A*, slight downward slipping of capital epiphysis of right femur. *B*, irregular fracture in cartilage plate of capital epiphysis. Note focal cystic changes as well as hemorrhage in cartilage ( $\times 50$ ). *C*, endochondral ossification proceeding from epiphyseal and metaphyseal surfaces of upper cartilage plate ( $\times 50$ ). *D*, fibrous bone formation in intertrabecular spaces in metaphysis ( $\times 100$ ).

Fig. 6.—*A*, articular cartilage of head of femur of calf extending over superior surface of femoral neck. *B*, coronal section through specimen shown in figure 6*A*. Note thick layer of hyaline cartilage covering neck of femur at *n*. Area *h* denotes femoral head and *g.t.*, greater trochanter. *C*, photomicrograph of specimen shown in figure 6*B*. Note course of epiphyseal cartilage plate and layer of cartilage on superior surface of neck of femur;  $\times 4$ .

ossification, may be considered as secondary to the fracture of the epiphyseal plate.

The cause of the fracture of the epiphyseal plate can perhaps be best explained by considering, first, the anatomy and the ontogenesis of the femur and, second, the effect of abnormal weight-bearing forces on some of these structures.

In a new-born full term infant no centers of ossification are present either in the head of the femur or in the region of the greater trochanter. The cartilaginous head sits almost directly on the shaft of the femur. The upper portion of a femur in a child from 6 to 12 months old may show a bony center of ossification for the capital epiphysis. The cartilaginous neck, which is very short, is in normal coxa valga. At 3 years of age there is an upward expansion of the shaft corresponding to the neck which causes a tilting of the head. At this time, or occasionally earlier, the center of ossification at the site of the greater trochanter appears. The neck, which is at first entirely cartilaginous, now consists of bone covered on its superior cortex by hyaline cartilage. This layer of hyaline cartilage is continuous with the capital epiphyseal plate and the cartilage encircling the center of ossification at the site of the greater trochanter.<sup>5</sup> At 4 years of age the upper capital epiphysis rests on the entire width of the oblique plate (fig. 7 A). A coronal (superoinferior) section through the head and neck of a normal femur of a child of 4 or more years will show a slight prominence of the inferior angle of the neck (fig. 7 B),<sup>6</sup> which acts as a buttress preventing the capital epiphysis from slipping downward.

Little or no cartilage is normally present on the superior cortex of the neck of the femur of man at or past the age of 4 years.<sup>7</sup> A layer of young periosteum takes the place of the hyaline cartilage. It is important to note that the fibers from this periosteum run in a curved direction into the depths of the matrix of the upper femoral epiphyseal plate (fig. 7 C). This allows for direct union between the periosteum and the matrix of the upper epiphyseal plate. The junction between the

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5. In animals, such as the rabbit or the calf, the articular cartilage may normally cover part of the superior surface of the femoral neck (fig. 6A, B and C).

6. It is of interest that while in man the medial ossicle of the neck can be seen only when the head and neck are sectioned coronally, Thompson (quoted by Walmsley: *J. Anat. & Physiol.* 49:434, 1915) described in the seal a superficial bony prominence which is a continuation of the inferior surface of the neck of the femur to the under-surface of the head. This bony projection in the seal, running onto the head of the femur, is not covered by articular cartilage.

7. Interruption of the continuity of the epiphyseal plate in the neck of the femur is often initiated by the long Sharpey fibers of the attached capsule of the joint.



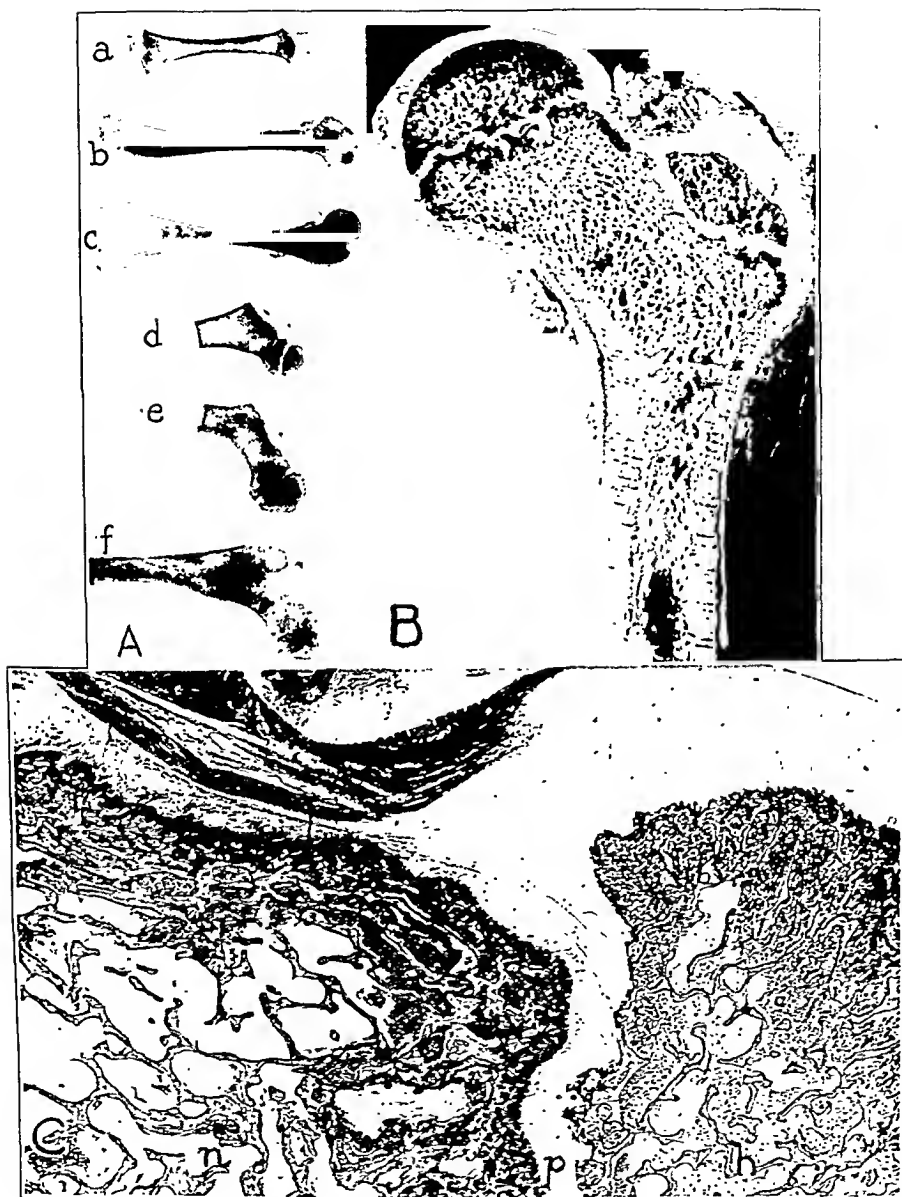


Fig. 7.—*A*, radiograph of proximal portions of femurs of children. Specimen *a* is from a new-born child; *b*, from a child 8 months old; *c*, from a child 18 months old; *d*, from a child 3 years old; *e*, from a child 5 years old, and *f*, from a boy 9 years old. Note inclination of cartilage plate of capital epiphysis. *B*, prominence or buttress (*x*) extending from inferior surface of neck of femur. Coronal section of upper portion of femur from a boy 9 years of age. *C*, photomicrograph showing arched fibers running from periosteum of neck of femur into matrix of upper epiphyseal plate and to contiguous bone trabeculae of epiphysis. *n* indicates neck; *h*, head, and *p*, cartilage plate of capital epiphysis;  $\times 4$ .



periosteum of the neck of the femur and the hyaline cartilage of the upper epiphysis is a weak area due to "tissue transition."

Additional structural changes exist. The neck increases in length, reaching its maximum ontogenetic size between the ages of 10 and 14 years. The normal coxa valga which is present in the young diminishes in this age period, and slipping of the upper capital epiphysis occurs at this time.

It would seem that the inferior buttress of the neck of the femur and the fibers linking the periosteum to the epiphyseal cartilage plate would prevent the head from slipping. As stated, the normal developmental and mechanical forces at the hip joint tend to produce a normal tilt of the upper epiphysis. Thus, an abnormal weight-bearing force, by

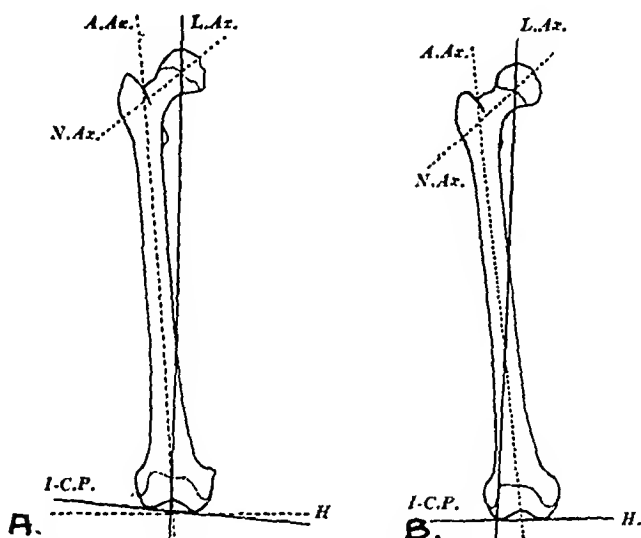


Fig. 8.—*A*, position of femur when feet are apart. The load axis (*L.Ax.*) passes through midcondylar point. Note that the infracondylar plane (*I.-C.P.*) slants upward and laterally. *B*, the load axis passes through lateral femoral condyle when feet are held together. Note that *H*, horizontal axis, coincides with infracondylar plane (after Walmsley).

destroying one or both of the normal barriers, may initiate the slipping of the capital epiphysis.

The weight-bearing forces acting on the hip joint are influenced to a great degree by the forces acting on the knee joint. Walmsley<sup>8</sup> has shown (fig. 8) that the weight-bearing line<sup>9</sup> through the femur passes through the lateral condyle when the patient stands with his feet together. With the feet spread apart, however, the load-axis passes

8. Walmsley, T.: The Vertical Axes of the Femur and Their Relations: A Contribution to the Study of the Erect Position. *J. Anat.* 67:284 (Jan.) 1933.

9. The weight-bearing line or load-axis is drawn from the center point of the femoral head perpendicular to the horizontal femoral infracondylar plane.

through the midcondylar point.<sup>10</sup> In the latter position the femur requires additional support, either muscular or otherwise, to overcome the shearing action at the knee joint.

The frequency of slipping of the capital epiphysis of the femur in boys of the Fröhlich type or in girls who are overweight may be due to the presence of an abnormal infracondylar plane. If the muscular support is weak, as is the case in obese boys of the Fröhlich type<sup>11</sup> or in girls who are very overweight, the heavy weight-bearing forces may play havoc on the femoral neck when the femur is in a position which requires additional muscular support. On the other hand, the presence of a longer femoral neck in the tall, thin, growing boy in whom there occasionally develops slipping of the capital epiphysis allows increased leverage action between the shaft of the femur and its neck. Thus, sudden abduction or adduction of the femur with the limb in hyperextension may injure the point of tissue transition on the superior surface of the neck.<sup>12</sup>

It seems possible that a crack or tear at the point of tissue transition on the neck of the femur would follow the course of the fibers of the periosteum into the upper epiphyseal plate. These fibers possibly prevent further progress of the fracture of the cartilage (preslipping stage). Additional trauma probably severs the periosteal fibers which join the upper epiphyseal plate. Additional changes are fracture of the atrophic buttress of the inferior cortex of the neck or compression of that projection. This is only part of the mechanism which initiates the slipping of the capital epiphysis. The activity of the muscles about the hip joint tends to separate the upper epiphysis completely from the neck.

#### DIFFERENTIAL DIAGNOSIS

Slipping of the capital epiphysis of the femur must be sharply differentiated from secondary coxa vara due to fractures, tumors, cysts or pathologic infiltrations, such as is seen in cases of Gaucher's disease. The congenital type of coxa vara may, if uncorrected in childhood, be mistaken for slipping of the capital epiphysis. In the

10. It has been noted in females that the femoral infracondylar line slants upward and medially when the knees are held together; with the feet apart, however, the line is horizontal. In boys or young men the femoral infracondylar line is horizontal when the knees are held together, and when the knees are apart it slants upward and laterally.<sup>8</sup>

11. Mikulicz, J.: Die seitlichen Verkrümmungen am Knie und deren Heilungsmethoden, *Arch. f. klin. Chir.* 23:560, 1879; 23:670, 1879.

12. Hutchinson, J.: On Detachment of the Epiphyseal Head of the Femur, *Arch. Surg.* 3:289, 1892. Poland, John: Traumatic Separation of the Epiphysis, London, Smith, Elder & Company, 1898. Rammstedt, C.: Ueber traumatische Lösung der Femurkopfeiphyse und ihre Folgeerscheinungen. *Arch. f. klin. Chir.* 61:559, 1900.

former condition the neck is much more involved than the capital epiphysis; in the latter, changes in the angle of the neck to the femur are secondary to the position of the capital epiphysis.

It is especially important to differentiate Perthes' disease from slipping of the capital epiphysis of the femur. Perthes' disease is characterized by aseptic necrosis of the capital epiphysis without any great disturbance to the epiphyseal plate. Changes in the shape of the slipped capital epiphysis are secondary to mechanical factors and are not part of the disease.

#### CONCLUSIONS

The tissues removed surgically from three patients with slipping of the capital epiphysis of the femur were examined microscopically. They exhibited evidence that the condition is one of a fracture through the upper femoral epiphyseal plate and contiguous trabeculae of bone. No definite evidence of primary degeneration of the epiphyseal plates was seen. Variations in the weight-bearing forces at the hip joint may be a predisposing factor in the causation of the fracture. The normal tilting of the capital epiphysis, which is the result of normal developmental and mechanical forces, is the basis for the condition.

## EXPERIMENTAL SHOCK

THE EFFECTS OF EXTRACTS FROM TRAUMATIZED LIMBS ON  
THE BLOOD PRESSURE

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AND

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Of the various theories suggested as to the mechanism of traumatic shock, two have recently received most attention, viz: (1) that of the absorption of metabolic toxins from the traumatized area with secondary generalized vasodilatation and increased permeability of the capillaries, a theory advocated by Cannon,<sup>1</sup> Cannon and Bayliss,<sup>2</sup> and others, and (2) that of the local loss of blood or plasma, or both, resulting in a serious decrease in the volume of circulating blood, as supported by the work of Blalock,<sup>3</sup> Phemister and co-workers,<sup>4</sup> Freedlander and Lenhart<sup>5</sup> and others.

Various investigators (Mason and Lemon,<sup>6</sup> Carlson, Woelfel and Powell,<sup>7</sup> Popielski<sup>8</sup> and Bayliss<sup>9</sup>) have shown that extracts of many

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From the Department of Surgery, the University of Chicago.

This study was aided by a grant from the Douglas Smith Foundation for Medical Research of the University of Chicago.

1. Cannon, W. B.: *Traumatic Shock*, New York, D. Appleton & Company, 1923.

2. Cannon, W. B., and Bayliss, W. M.: Note on Muscle Injury in Relation to Shock, Medical Research Council, Spec. Res. Ser. no. 26, London, His Majesty's Stationery Office, 1919, p. 19.

3. Blalock, A.: The Cause of the Low Blood Pressure Produced by Muscle Injury in Dogs, *Arch. Surg.* **20**:959 (June) 1930.

4. Parsons, E., and Phemister, D. B.: Haemorrhage and Shock in Traumatized Limbs, *Surg., Gynec. & Obst.* **51**:196 (Aug.) 1930. Roome, N. W.; Keith, W. S., and Phemister, D. B.: The Effect of Bleeding After Reduction of the Blood Pressure by Various Methods, *ibid.* **56**:161 (Feb.) 1933.

5. Freedlander, S. O., and Lenhart, C. H.: *Traumatic Shock*, *Arch. Surg.* **25**:693 (Oct.) 1932.

6. Mason, E. C., and Lemon, C. W.: Autointoxication and Shock, *Surg., Gynec. & Obst.* **53**:60 (July) 1931.

7. Carlson, A. J.; Woelfel, A., and Powell, W. H.: A Possible Hormone Vasomotor Mechanism, *Proc. Am. Physiol. Soc.*, 1908, p. 23.

8. Popielski, L.: Ueber die physiologische Wirkung von Extrakten aus sämtlichen Teilen des Verdauungskanales, *Arch. f. d. ges. Physiol.* **128**:191, 1909.

9. Bayliss, W. M.: *Principles of General Physiology*, ed. 4, New York, Longmans, Green & Co., 1924, p. 701.

tissues contain substances which depress the blood pressure, and this fact has been frequently cited<sup>10</sup> in support of the "toxic theory" of traumatic shock. Carlson, Woelfel and Powell,<sup>7</sup> however, after examining saline extracts of a large variety of tissues, found that the extracts of muscle were among the least toxic of the preparations studied. Little attention has been called to the presence in extracts of muscle and other tissues of pressor substances, although the existence of such substances was demonstrated as early as 1898 by Tigerstedt and Bergman.<sup>11</sup> Collip,<sup>12</sup> who more recently studied extracts of a wide variety of tissues, found that both pressor and depressor substances were usually contained in such extracts and that either type of substance could be obtained at will by fractionations with acetone. In fact, by concentration extracts were obtained which when administered to animals caused rises in blood pressure up to 350 mm. of mercury.

The extracts studied by most of the aforementioned investigators were prepared from normal tissues by various chemical extractions. The present experiments were undertaken to determine the effects on the blood pressure of extracts of the muscles of traumatized limbs prepared by rapid mechanical extraction by means of a hydraulic press.

#### EXPERIMENTAL PROCEDURE

*Series 1: Injection of Extracts of Traumatized Muscle into a Jugular Vein.*—  
(A) Injection of Uncentrifugated Extracts into a Normal Dog: Six experiments were carried out in the following manner on dogs under ether anesthesia: One hindleg was traumatized repeatedly with a padded hammer until a sustained fall in blood pressure occurred; care was taken to avoid breaking the skin or the bones of the leg. After a period of from forty-five to seventy-five minutes, when the blood pressure remained at levels of from 50 to 70 mm. of mercury, a tourniquet was applied about the traumatized limb at the level of the hip joint, and the limb was amputated approximately 2 cm. below the tourniquet. The skin was removed, and the muscles were dissected from the bones. A large amount of unclothed bloody fluid was invariably obtained during the dissection. This fluid and the muscle tissue were passed through a meat chopper and extracted in a hydraulic press at a pressure of from 350 to 375 Kg. per square centimeter. The extract contained globules of fat and small particles of tissue. In each experiment a second dog was anesthetized with ether and the extract introduced into a jugular vein. Sudden death of the second dog resulted in all the experiments. At autopsy intravascular clotting in the heart and pulmonary arteries was found in four dogs, and pulmonary fat embolism was demonstrated by the gross and

10. Moon, V. H., and Kennedy, P. J.: Pathology of Shock, Arch. Path. **14**: 360 (Sept.) 1932. Cannon.<sup>1</sup> Mason and Lemon.<sup>6</sup>

11. Tigerstedt and Bergman: Skandinav. Arch. f. Physiol. **8**:223, 1898; cited by Collip.<sup>12</sup>

12. Collip, J. B.: A Non-Specific Pressor Principle Derived from a Variety of Tissues, J. Physiol. **66**:416 (Dec.) 1928.

microscopic appearances in the remaining two animals. For this reason the procedure of centrifugating the extract to remove the fat and fragments of solid tissue and the administration of heparin to prevent clotting was adopted in all the subsequent experiments.

(B) Injection of Centrifugated Extracts into a Heparinized Dog: In four experiments extracts were prepared by the technic described, and centrifugated to remove the fat and particles of tissue. The top layer of fat was pipetted off and the homogeneous, wine-red middle layer was used for perfusion. In three experiments a second dog was anesthetized with ether and given sufficient heparin (approximately 30 mg. per kilogram of body weight) to render the blood incoagulable; the extract was then introduced into a jugular vein. The reaction of the blood pressure was variable; in one case there was a depression in blood pressure of 36 mm. of mercury, and in two cases there was a rise of 27 and 58 mm. of mercury, respectively. In all the experiments a rapid resumption of the previous "normal" level of the blood pressure occurred in from three to four minutes.

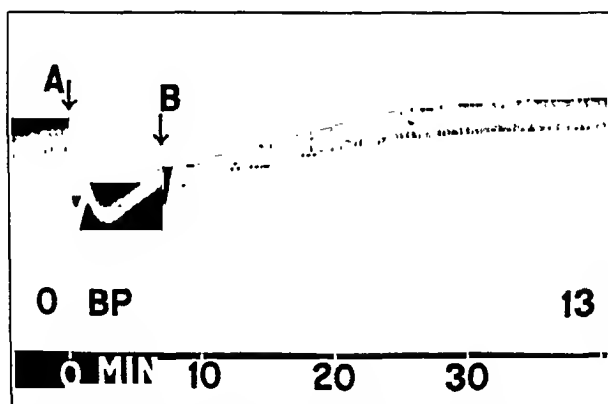


Fig. 1 (experiment 13).—Kymograph tracing showing the effects on the blood pressure of returning to an animal, by vein, the extract obtained from its traumatized leg. The blood pressure was 122 mm. of mercury before the leg was traumatized, 88 mm. when the extract was given (95 cc. was given at A and 15 cc. at B). The blood pressure fell to 48 mm. but rose again to 88 mm. eighteen minutes after the administration of the first dose of extract and was 113 mm. three hours later.

In one experiment 110 cc. of the extract was injected into the animal from which it had been obtained, heparin being given just before administration of the extract. The blood pressure fell immediately 43 mm.; it then returned in eighteen minutes to the level observed before administration of the extract and in three hours to that existing before traumatism (fig. 1).

The rise in blood pressure on administration of the extract when it occurred in this group of experiments was possibly due to the sudden addition to the blood volume. To test the effect on the blood pressure of the introduction of similar amounts of whole blood, three animals weighing from 10 to 13 Kg. were given by the same method from 225 to 300 cc. of heparinized blood. The blood pressure rose in each from 16 to 35 mm. of mercury and returned to approximately its previous resting level in from six to eight minutes. Thus the pressor effects

caused by the intravenous injection of the extract in some cases were similar to the effects of a transfusion of whole blood. Other factors to be considered as causes of the rise in blood pressure are: 1. The increased production of epinephrine during the trauma and the storage of this substance in the exudate in the leg, with subsequent extraction. 2. The vasoconstrictor properties of traumatized blood, as described by Phemister and Handy.<sup>13</sup> These properties, however, were found by the authors just cited to be inadequate to cause a rise in systemic blood pressure. 3. Effects of temperature, i. e., vasoconstriction due to

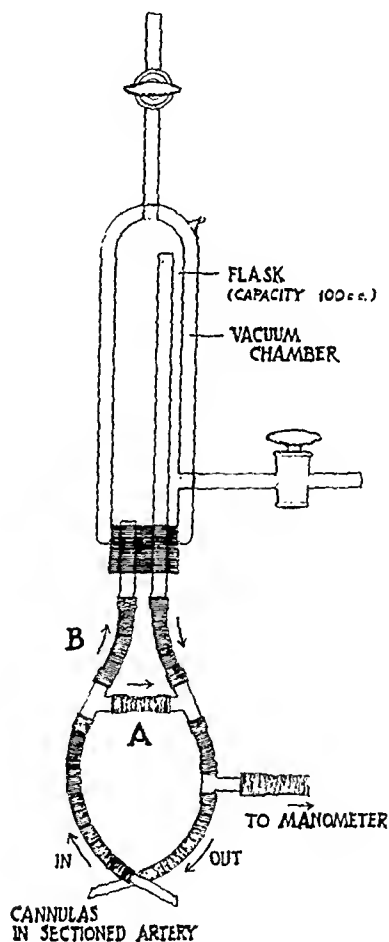


Fig. 2.—Modified Anrep viviperfusion apparatus used for administration of the extract without changes in the volume of circulating blood. The rubber tube is clamped at point *B* and open at *A* during the preparation of the experiment; perfusion occurs when the tubing is released at *B* and clamped at *A*.

the perfusion of cold material. This was ruled out by careful control of the temperature of perfused material in two experiments, in which the rises in blood pressure persisted. 4. The presence of pressor substances in the extract, as described by Collip.<sup>12</sup>

The question as to the effect of epinephrine was investigated and discarded by reason of the following experiments: In two dogs, the adrenal glands were totally excised, and after the animals had a period of rest of from one and a half to two hours, one hindleg of each was traumatized and amputated, and the muscle was

13. Phemister, D. B., and Handy, J.: Vascular Properties of Traumatized and Laked Bloods, *J. Physiol.* 64:155 (Nov.) 1927.

extracted as previously described. The perfusion of the extract into a second dog of similar weight by means of a cannula inserted in a jugular vein resulted in both instances in a transient minor depression followed by a considerable rise in blood pressure. The rise in one case amounted to 90 mm. of mercury and was followed by a return to the resting level in from nine to ten minutes. It was then thought that the pressor effect observed in these experiments was due chiefly to the large sudden increase in the volume of the circulating blood or to the presence of pressor substances.

*Series 2: Viviperfusion Experiments.*—To eliminate the factor of increased blood volume, the following series of experiments was performed, using a modified Anrep viviperfusion apparatus<sup>12</sup> (fig. 2).

### Summary of Viviperfusion Experiments

Experiment Number	Weight of First Dog, Kg.	Blood Pressure When Limb Was Amputated, Mm. of Mercury	Weight of Traumatized Muscle Obtained, Gm.	Volume of Extravasated Fluid and Extract, Cc.	Fluid Recovered, Percentage of Calculated Blood Volume	Weight of Second Dog, Kg.	Changes in Carotid Blood Pressure, Mm. of Mercury
							(a) On Perfusion of the Total Extract
15	16.6	65	796	390	31.5	9.6	Plus 26
16	18.6	70	582	250	18.0	12.1	Plus 8
17	12.4	30	424	...	....	17.8	Plus 15
18	9.7	49	440	178	24.6	19.0	Plus 19
25*	10.75	46	...	...	....	13.9	Plus 17
							(b) Fractionations
							Perfusion of Extravasated Fluid      Perfusion of Muscle Extract
19	24.0	46	770	540	30.1	9.5	Plus 17 (Clotted)
20	15.5	68	597	165	14.3	15.5	Plus 11 No change
21	23.0	36	...	...	....	14.0	(Clotted) Minus 41
22	10.5	41	...	...	....	16.1	Plus 7 Minus 10
23	12.5	36	...	...	....	13.0	Plus 15 Minus 8
24	11.5	50	319	205	24.0	10.84	No change Minus 5
26	23.2	91	1,189	603	35.0	18.5	No change Minus 21

\* In this experiment adrenalectomy was performed one and a half hours before the dog's limb was traumatized.

† Calculated as one thirteenth of the body weight.

Twelve dogs weighing from 9.7 to 24 Kg. were anesthetized, some receiving ether and a few, sodium barbital administered intravenously. One hindleg was traumatized and amputated when the blood pressure remained at levels of from 36 to 91 mm. of mercury. The muscles were extracted in the hydraulic press as described, with the exception that in seven experiments the bloody fluid which exuded during dissection was removed and the muscles extracted separately.

In each experiment a second dog, usually of similar or lesser weight, was anesthetized with ether or with sodium barbital administered intravenously and given sufficient heparin (approximately 40 mg. per kilogram of body weight) to render the blood incoagulable. An Anrep viviperfusion flask of 100 cc. capacity was then inserted in a femoral artery. The use of this viviperfusion flask permitted the administration of large amounts of the extract without increasing the volume of circulating blood. The general blood pressure was measured and



recorded by means of a cannula inserted in the carotid artery and connected to a mercury manometer, and the blood pressure distal to the perfusion flask was similarly recorded. In three experiments (15, 18 and 21) a plethysmograph was placed on the leg distal to the perfusion flask. In experiment 25 the first dog was prepared by total adrenalectomy one and a half hours before being traumatized, and the experiment was then continued as described.

A summary of the experiments and of the results obtained is given in the table, and typical kymograph tracings are given in figures 3, 4, 5 and 6. In each of the five experiments in which the extract perfused was obtained from the combined bloody fluid and the muscles, there was a rise of the blood pressure of from 8 to 26 mm. of mercury. In the two experiments (15 and 18) of this group

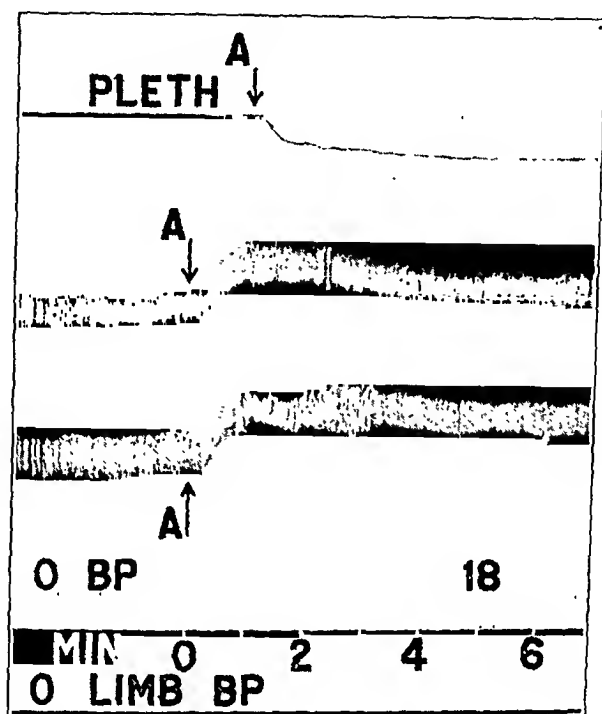


Fig. 3 (experiment 18).—Kymograph tracings showing the effects on the blood pressure of a dog of viviperfusion of the total extract from the traumatized limb of another dog. One hundred cubic centimeters of extract was given at *A*; note that there was a rise in blood pressure of 19 mm. of mercury in both the general blood pressure and the blood pressure of the limb, with a concurrent diminution of the volume of the limb, as indicated in the uppermost curve, marked *pleth*.

in which plethysmographic studies were made, there was a diminution of the volume of the limb simultaneous with the rise in the blood pressure.

In the seven experiments in which the bloody fluid and the extract of muscle were separated, the perfusion of the bloody fluid resulted in a rise of the general blood pressure of from 7 to 17 mm. of mercury in four experiments; no change of general blood pressure resulted in two experiments (in one of which there was a rise of 5 mm. of mercury in the blood pressure of the limb) while clotting prevented taking the measurement in the seventh experiment. In five experiments

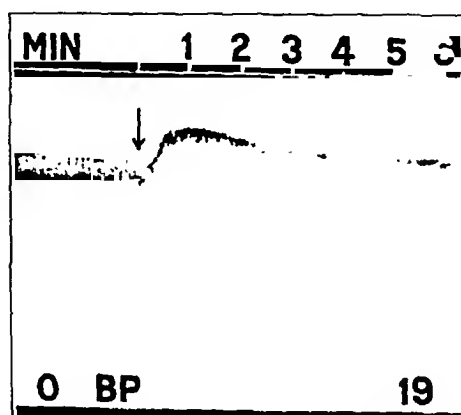


Fig. 4 (experiment 19).—Kymograph tracing showing the effects on the blood pressure of viviperfusion of the extravasated bloody fluid from the traumatized limb. Note the rise in blood pressure of 17 mm. of mercury after a preliminary slight depression following the administration of the extract, as indicated by the arrow.

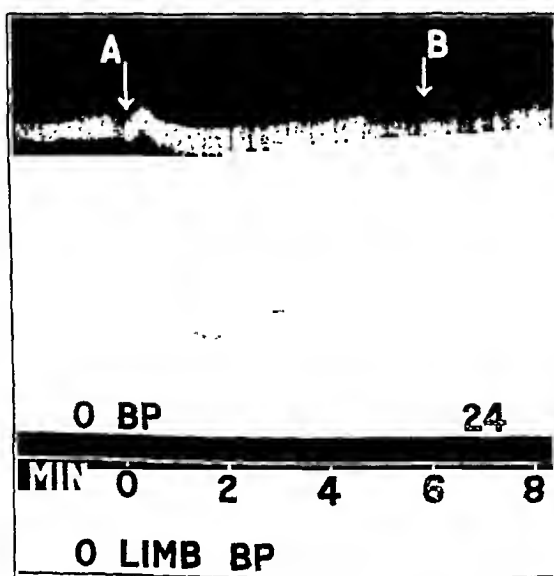


Fig. 5 (experiment 24).—Kymograph tracings showing the effects on the blood pressure of viviperfusion of the extract obtained from the muscles alone from a traumatized limb. Note the slight rise in general blood pressure, as shown in the upper curve, followed by a depression of 5 mm. of mercury, and the more pronounced fall in blood pressure of the limb, as shown in the lower curve, indicating local vasodilatation.

the administration of the extract of muscle alone produced a fall in blood pressure of from 5 to 41 mm. of mercury; no change in the blood pressure occurred in the sixth experiment, and clotting occurred in the seventh. In experiment 21 there was no marked change in the volume of the limb incident on the perfusion of either the bloody fluid or the extract of muscle.

In all cases the alteration of the blood pressure was transient, recovery to the previous level beginning before completion of the perfusion and being complete usually within from five to eight minutes. In no case was there a depression in the blood pressure of any permanence. The results of the experiment in which preliminary adrenalectomy was performed were similar to those of the remaining experiments of the corresponding series.

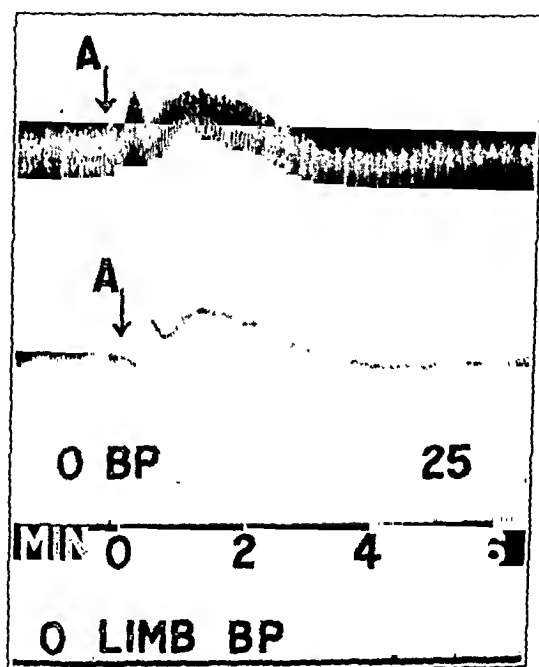


Fig. 6 (experiment 25).—Kymograph tracings showing the effects on the blood pressure of an extract prepared from an adrenalectomized dog. One hundred cubic centimeters of the extract was given at *A*; note the resulting marked biphasic rise in blood pressure.

#### COMMENT

The extracts of tissue studied by the investigators cited previously were usually prepared by the use of solvents, by boiling or by concentration methods. Many of these extracts have been reported as toxic and were found capable of causing death in some cases. It must be conceded, however, that the methods of preparation were frequently not physiologic and may have been capable of so altering the materials present in the extract as to increase its toxicity. Collip<sup>12</sup> has shown that most tissues contain both pressor and depressor substances, and either type of material can be concentrated and purified at will. In the present experiments

extraction was carried out by means of a hydraulic press, a rapid and entirely mechanical method; hence the concentrations of the various hemodynamic substances would be expected to remain in much the same proportions in the extract as in the original tissue.

The most toxic of the extracts of tissue studied by previous investigators were those of such tissues as lung and liver, while the extracts of muscle were found to be among the least toxic. Yet the toxicity of such extracts has been cited as evidence in favor of the toxic theory of traumatic shock, although cases of large injuries to muscles are the ones in which shock most commonly occurs, and the lungs and liver are seldom concerned. For this reason traumatized muscle was used as the source of the extracts studied in the present experiments, the degree of "shock" induced by the trauma being controlled by direct readings of the blood pressure.

In the first series of experiments it was demonstrated that extracts prepared as described had marked blood-coagulating properties and that this factor was sufficient to kill instantly the animal to which the extract was given by way of a jugular vein, death resulting from intravascular clotting. Also the crude extract was found to contain sufficient particles of fat and of tissue to cause sudden death by pulmonary embolism in several cases. These properties of muscle extracts may be an additional explanation of the "toxicity" observed by certain other workers.

In the final series of experiments the extract was purified by centrifugation; the recipient was heparinized, and the extract was administered by a viviperfusion method, by which alteration of the volume of circulating blood was prevented. In these experiments it was found that the perfusion of a total extract of the extravasated blood and the muscles of a traumatized limb invariably caused a slight transient rise in blood pressure. On fractionation of the extract by separation of the bloody fluid obtained during dissection of the limb, a rise in blood pressure was usually found to occur when the bloody fluid was perfused. When the extract of muscle only was perfused there was a slight to moderate depression in blood pressure in most cases. The depressor responses were of magnitudes similar to those observed with perfusion of extracts of normal muscle. In both groups of experiments the alterations in blood pressure were transient, a return to the resting level occurring within a few minutes; in no case did a permanent depression in blood pressure or death of the animal occur during the period of observation (from two to six hours). Thus only a moderate degree of toxicity was demonstrated for extracts of traumatized muscle prepared in a hydraulic press, and in fact the total extract was invariably pressor in its effect. No support for the toxic theory of traumatic shock can therefore be adduced from these experiments.

The explanation of the rises in blood pressure observed seems to be the presence of the "non-specific pressor substance" studied by Collip,<sup>12</sup>

since the effects of temperature and volume were ruled out by the methods used, and Phenister and Handy<sup>13</sup> could demonstrate no such marked vasoconstrictor effects by the viviperfusion of blood traumatized in vitro. The possibility of excess secretion of epinephrine in the first animal with storage in the limb and subsequent extraction seems ruled out by the results of the three experiments performed after preliminary total adrenalectomy, in which marked rises of the blood pressure occurred. Many of the kymographic tracings showed a biphasic character to the reaction curve of perfusion of both muscle and combined extracts, presumably indicating that these extracts contain a mixture of hemodynamic substances.

A study of the amounts of muscle and of extract obtained (table) showed that from 14.3 to 35 per cent of the total volume of blood (calculated as one thirteenth of the body weight) was recovered from the traumatized limb. Because of the level of amputation and of the losses inherent in extraction not all the fluid lost into the limb was recoverable; hence the total amount of fluid, which appeared to be chiefly blood, is considerably greater than that indicated by the figures given and represents a large local loss from the circulation.

#### SUMMARY AND CONCLUSIONS

Experiments on dogs are described in which extracts obtained by means of a hydraulic press from the tissues of a traumatized limb were perfused in a second animal. Preliminary experiments indicated that such extracts were markedly hemocoagulant and contained particles of fat and of tissue, and that the extract almost invariably caused death when administered intravenously to a second animal; hence in the final series of experiments the extracts were purified by centrifugation, and the recipient was heparinized.

It was found that the intravenous administration of the total extract (i. e. extract prepared from both the bloody extravasated fluid and the muscles) invariably caused rises in blood pressure in the recipient animal. When the bloody fluid was given alone the rises were again frequently observed, while the use of the extract of muscle alone usually resulted in minor depressions in blood pressure.

It was concluded from these experiments that: 1. Centrifugated extracts of traumatized limbs obtained by means of a hydraulic press caused no depression in blood pressure when perfused as a whole in a second (heparinized) animal; instead, rises in blood pressure occurred. 2. Similar extracts of the traumatized muscles alone (after removal of the extravasated bloody fluid obtained during dissection) were slightly toxic but did not cause a sustained fall in blood pressure or death. 3. The findings do not support the "toxic theory" of the etiology of traumatic shock.

# BACTERICIDAL EFFECT OF HIRUDIN AND HEPARIN

## II. GROWTH OF ORGANISMS IN BLOOD RENDERED INCOAGULABLE WITH HIRUDIN AND HEPARIN

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In another paper,<sup>1</sup> we reported the effects of the application of leeches and of the intravenous injection of hirudin and heparin on bacteremia induced in dogs by the intravenous injection of a suspension of staphylococci. We became interested in this investigation because of the good results we obtained with leeches in the treatment of phlebitis and because of the report by Bosc and Delezenne<sup>2</sup> in which the authors stated that animals are protected from bacteremia by the intravenous injection of hirudin and that in vitro there is an inhibition of the growth of organisms in blood to which hirudin has been added. We conducted both in vivo experiments (on dogs) and in vitro experiments to determine if we could demonstrate such an effect of hirudin on the growth of organisms in blood. Our in vitro experiments are reported in this paper.

### EXPERIMENTS

*Experiment 1.*—Nine sterile test tubes were used. The experiment was conducted under aseptic conditions.

In test tubes 1, 2 and 3 was placed 0.5 cc. of an aqueous solution of potassium oxalate, containing 2 mg. of potassium oxalate per cubic centimeter. In test tubes 4, 5 and 6 was placed 0.5 cc. of an aqueous solution of hirudin containing 2 mg. per cubic centimeter. Five-tenths cubic centimeter of an aqueous solution of heparin containing 0.5 mg. heparin per cubic centimeter was pipetted into each of the remaining three test tubes (7, 8 and 9). In each of the nine tubes was then placed 1 cc. of freshly drawn uncoagulated human blood. One-tenth cubic centimeter of a suspension of staphylococci was added to each tube. The suspension of staphylococci was made by washing the forty-eight hour growth on agar culture plates in physiologic solution of sodium chloride. Each tube was shaken to mix the contents, and all the tubes were placed in an incubator. There was no clotting in any of the tubes. After twenty-four hours the same amount of melted agar

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From the Department of Surgery, Tulane University School of Medicine.

1. Ochsner, Alton, and Mahorner, Howard R.: Bactericidal Effect of Hirudin and Heparin: I. Intravenous Injection of Hirudin and Heparin and Leeching in Experimental Bacteremia, *Arch. Surg.* **31**:308 (Aug.) 1935.

2. Bosc and Delezenne: Imputrescibilité du sang rendu incoagulable par l'extrait de sangsue, *Compt. rend. Acad. d. sc.* **123**:465, 1896; idem: De l'immunité conférée par quelques substances anticoagulantes. De son mécanisme: excitation de la phagocytose augmentation du pouvoir bactéricide du sang, *ibid.* **123**:500, 1896.

culture medium at a temperature of 42 C. was mixed with the contents of each tube and then poured into Petri dishes. At the time of this transfer it was noted that a part of the blood in tube 5 had coagulated. This clot in one of the tubes containing hirudin was too small to interfere with the results. The nine Petri dishes were placed in an incubator, and the mixture in them was observed at frequent intervals for eleven days. Whitish irregular colonies were noted on all the plates. Although there was slight variation in the number of colonies in the different areas throughout the plates, the number was approximately the same for each plate. There was no appreciable difference in the rate of growth or the character or number of colonies in the plates containing solutions of potassium oxalate (1, 2 and 3), those containing solutions of hirudin (4, 5 and 6) or those containing solutions of heparin (7, 8 and 9).

The conclusion reached was that the addition of hirudin and heparin does not affect the growth of staphylococci in blood.

*Experiment 2.*—The experiment was conducted under aseptic conditions. Eight test tubes were used. In each of the first four tubes (1, 2, 3 and 4) was placed 0.5 cc. of an aqueous solution of hirudin containing approximately 1 mg. of hirudin per cubic centimeter. In the remaining four tubes (5, 6, 7 and 8) was placed 0.5 cc. of an aqueous solution of sodium citrate containing 2 mg. of sodium citrate per cubic centimeter of solution. There was no clotting in any of the test tubes. To one of the tubes containing hirudin (tube 1) and one containing sodium citrate (tube 5) was immediately added 0.1 cc. of the suspension of staphylococci. After nine hours, 0.1 cc. of the staphylococcus suspension was added to another of the tubes containing hirudin and 0.1 cc. to one of the tubes containing sodium citrate (tubes 2 and 6, respectively). After twenty-four hours, 0.1 cc. of the staphylococcus suspension was added to another tube containing citrate and 0.1 cc. to a tube containing hirudin (tubes 3 and 7, respectively), and after forty-eight hours, 0.1 cc. of the suspension was added to the last tube containing hirudin and 0.1 cc. to the last tube containing citrate (tubes 4 and 8, respectively). All tubes were kept in the incubator after they were prepared.

Twenty-four hours after the addition of the staphylococcus suspension to each tube, the contents of each was mixed with melted agar peptone culture medium at 42 C. and transferred to a Petri dish. The same amount of medium was used for each tube. The tubes were replaced in the incubator and observed daily.

Colonies appeared in each plate. No difference in the character or the approximate number of colonies was observed between any of the plates containing hirudin and the controls containing sodium citrate.

The conclusion was that hirudin has no inhibitory effect on the growth of staphylococci in blood, even if the organisms are added at various periods up to forty-eight hours after the hirudinization of the blood.

*Experiment 3.*—The experiment was conducted under aseptic conditions. Twelve test tubes were used (see table). In tubes 1, 2 and 3 were placed 0.5 cc. of physiologic solution of sodium chloride (0.9 per cent) and 0.5 cc. of freshly drawn blood mixed with sodium citrate crystals. In tubes 4, 5 and 6 were placed 0.5 cc. of a solution of hirudin in physiologic solution of sodium chloride and 5 cc. of the solution containing ten crystals of the hirudin.

In three tubes, 7, 8 and 9, were placed 0.5 cc. of a solution of heparin in physiologic solution of sodium chloride, and 30 cc. of the solution containing 3 mg. of heparin. In tube 10 were placed 0.5 cc. of freshly drawn blood and 0.5 cc. of physiologic solution of sodium chloride; in tube 11 were placed, 0.5 cc. of freshly drawn blood and 0.5 cc. of the solution containing hirudin and in tube 12, 0.5 cc.

of freshly drawn blood and 0.5 cc. of the solution containing heparin. To each of the twelve tubes was then added 0.1 cc. of a suspension of staphylococci in physiologic solution of sodium chloride. The contents of each tube were quickly mixed with approximately the same quantity of melted peptone agar culture medium at 42 C. and transferred to a Petri dish. No clotting occurred in any of the tubes, even in tube 10, which was without an anticoagulant. The twelve Petri dishes were placed in the incubator. The type of colonies developing on the plates was the same. They were counted through a square millimeter window at the end of twenty-four and seventy-two hours. There was not enough difference between the average counts and size of the colonies in the different plates to conclude that there was any inhibition of growth on any of the plates. At the end of twenty-four hours, the lowest count for colonies per twenty square millimeters was in plate 9

*Table Showing the Results of Experiment 3 from Growing Staphylococci in Hirudinized Blood\**

Tube	Contents of Tubes†	Colonies after 24 Hours	Average	Colonies after 72 Hours	Average	Total Average
1	0.5 cc. physiologic solution of sodium chloride; 0.5 cc. citrated blood.....	56-47	51.5	74-58	61	56.25
2	0.5 cc. physiologic solution of sodium chloride; 0.5 cc. citrated blood.....	42-45	43.5	42-36	39	41.25
3	0.5 cc. physiologic solution of sodium chloride; 0.5 cc. citrated blood.....	61-44	50.5	58-57	57.5	54
4	0.5 cc. hirudin; 0.5 cc. citrated blood..	50-39	44.5	56-41	48.5	46.5
5	0.5 cc. hirudin; 0.5 cc. citrated blood..	43-43	43	50-54	52	47.5
6	0.5 cc. hirudin; 0.5 cc. citrated blood..	47-66	56.5	78-45	61.5	59
7	0.5 cc. heparin; 0.5 cc. citrated blood..	39-59	49	74-50	62	55.5
8	0.5 cc. heparin; 0.5 cc. citrated blood..	33-58	35.5	54-46	50	42.75
9	0.5 cc. heparin; 0.5 cc. citrated blood..	22-32	27	47-34	40.5	33.75
10	0.5 cc. uncoagulated blood inoculated with bacteria; 0.5 cc. physiologic solution of sodium chloride.....	66-33	49.5	93-61	57	63.5
11	0.5 cc. uncoagulated blood inoculated with bacteria; 0.5 cc. hirudin.....	41-90	65.5	71-104	87.5	76.5
12	0.5 cc. uncoagulated blood inoculated with bacteria; 0.5 cc. heparin.....	48-65	56.5	100-76	88	72.25

\* The preparations used contained 3 mg. of heparin to 20 cc. of physiologic solution of sodium chloride and 10 crystals of hirudin to 5 cc. of physiologic solution of sodium chloride.

† The contents of the tubes were transferred to melted peptone agar culture mediums immediately after the addition of the hirudin, or of heparin, and staphylococci.

(heparin), averaging 27 colonies, whereas the highest count was in plate 12 (heparin) averaging 56.5 colonies.

After seventy-two hours plates 1, 2 and 3 averaged 50.5 colonies per twenty square millimeters; plates 4, 5 and 6 averaged 51 colonies, and plates 7, 8 and 9 averaged 44 colonies. There was an average of 68.5 colonies per twenty square millimeters in plate 10 (without an anticoagulant), but plates 11 (hirudin) and 12 (heparin) averaged 76.5 and 72, respectively.

#### SUMMARY

In test tubes a suspension of staphylococci was added to hirudinized blood, to heparinized blood, to citrated blood and to blood mixed with physiologic solution of sodium chloride. Three sets of experiments were run, in one the addition of the staphylococci being delayed for periods



up to forty-eight hours after the blood was hirudinized or citrated. In another the blood was incubated for twenty-four hours after the addition of hirudin, or heparin, and of staphylococci before being transferred to the agar plate culture medium. In a third experiment the blood was transferred to agar plates immediately after the addition of the hirudin, or heparin, and the staphylococci.

#### CONCLUSION

Rendering blood incoagulable with hirudin does not inhibit the growth of staphylococci in blood in vitro.

## PURULENT PERICARDITIS

REPORT OF FIVE CASES IN WHICH TREATMENT WAS BY PERI-  
CARDIOTOMY, AND REVIEW OF THE LITERATURE FROM  
APRIL 30, 1927, TO JAN. 1, 1934

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AND

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If unrecognized, purulent pericarditis kills the patient. The patient in whom the condition is diagnosed and who is treated expectantly or by therapeutic aspiration fares no better. Operative attack is the only method at one's disposal which offers any chance to cope successfully with the condition.

In spite of a fair percentage of cures from surgical measures, and in spite of the conspicuous reviews of Roberts, Porter, Eliot, Rhodes, Poole and Alexander on the advantages of pericardiotomy when contrasted with the impotence of less radical means, the number of cases in which pericardiotomy is performed for pyopericardium is small. In 1927, we<sup>1</sup> could assemble only 128 cases. Of these, 118 were culled from the literature; 9 were contributed from the surgical services of the University Hospital, and 1 was reported through the courtesy of Dr. Harvey B. Stone.

In view of the not infrequent occurrence of the lesion, we feel that the problem of its treatment is well worth further discussion, especially as no one has had a broad operative experience with the condition. First, we wish, however, to place on record five other cases<sup>2</sup> in which we treated the condition by incision and drainage.

### REPORT OF CASES

CASE 1.—A white girl, aged 19 years, was admitted to the Emergency Hospital, Annapolis, Md., March 2, 1929, was operated on, March 7, and was discharged, April 27. She had been sick for a month and very ill for several weeks before admission. Her attack began as one of acute bronchitis followed by pneumonia. An empyema did not develop. A diagnosis of suppurative pericarditis was made because of the character of her breathing and the paradoxical pulse, and because the x-ray picture showed an enlarged pericardial shadow.

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From the Department of Surgery, School of Medicine, University of Maryland.

1. Winslow, N., and Shipley, A. M.: Pericardiotomy for Pyopericardium, *Arch. Surg.* **15**:317 (Sept.) 1927.

2. Four of these cases have been briefly described by Truesdale, P. E.: Low Pericardiotomy for Acute Suppurative Pericarditis, *New England J. Med.* **208**: 671, 1933 (cases 21, 22, 23 and 24, p. 677).

At operation, 8 ounces (236 cc.) of thin purulent fluid escaped, from which a streptococcus grew out in culture. The operative approach was by the chondro-xiphoid route. When the pericardium was opened, pus gushed from the incision. Two tubes for irrigation with surgical solution of chlorinated soda were left in the pericardium for drainage. For several days after the operation, the patient's condition was desperate. On the fourth day irrigations were begun by introducing the fluid into the pericardium through one tube and allowing it to escape through another. Following irrigation of the pericardium, the patient's condition improved.

The girl was a pupil nurse. After several months' convalescence, she returned to duty, finished her training and was graduated. For a year after the operation, she had some shortness of breath when she hurried or climbed stairs but these symptoms eventually disappeared. In May 1934 she was enjoying excellent health and had no manifest cardiac embarrassment.

CASE 2.—A white boy, aged 17 years, was admitted to the hospital, April 18, 1930, for cyanosis, shortness of breath and precordial pain of four days' duration. These symptoms followed an attack of scarlet fever which began three weeks before.

Examination disclosed a markedly enlarged cardiac area, an obtuse cardio-hepatic angle and a pericardial friction rub at the base of the heart. The cardiac sounds were distant at the apex, but were well heard at the base. The temperature was 102.2 F.; the pulse rate was 120, not paradoxical; the respiratory rate, 30; the blood pressure was 110 systolic and 60 diastolic. The white blood cells numbered 18,100, with a ratio of polymorphonuclears of 78, small lymphocytes 16, and large mononuclears 6 per cent, respectively. A blood culture was negative after seventy-two hours. A diagnosis of pericardial effusion was made. On the morning of April 19, with the patient under avertin anesthesia, a pericardiotomy was done by the combined transsternal and transchondral approach. An incision was made in the midline, extending from the level of the fourth rib to the junction of the second portion of the sternum with the ensiform process and was then curved outward over the edge of the costal margin for 3 inches (7.6 cm.). After the sternum and cartilages were uncovered, an opening was made with a bur through the sternum near its left margin and opposite the cartilage of the sixth rib. The hole was enlarged by rongeur and 2 inches (5 cm.) of the left fifth and sixth costal cartilages was removed. This gave a relatively large exposure through the triangle of safety. The left edge of the pleura was seen, but it was out of the way. The internal mammary vessels did not come into view. When the pericardium was opened, a large amount of seropurulent fluid escaped. It was easy to examine the pericardial sac for adhesions and pockets. A smear of the pus made at the operation showed no organisms, and a culture was negative. A smear made a few days later, however, showed the presence of staphylococci and gram-positive bacilli, and a culture yielded *Staphylococcus haemolyticus* and gram-positive bacilli. This, of course, may have been a contamination. No drainage was left in the pericardial sac; but several gauze drains were placed down to the opening in the pericardium.

The patient had a stormy postoperative course. His temperature continued high for nine days, ranging from 100 to 102 F., after which it gradually subsided. He has exhibited no signs of subsequent cardiac disability. It was felt that the boy would have had a better convalescence if drains had been put in the pericardium and irrigations had been resorted to.

This patient was operated on under tri-brom-ethylalcohol anesthesia. A relatively small dose was given and was supplemented by a 0.5 per cent solution

of procaine hydrochloride injected under the skin. The combination produced a very satisfactory anesthesia. It offers an advantage over general anesthesia in unruly children and nervous adults, but local anesthesia is preferable when it can be used.

CASE 3.—A 50 year old white man had been desperately sick for several weeks. His illness began as pneumonia in the left lung.

He was seen the day after admission to the hospital at Waynesboro, Pa., in consultation with his physician, who suspected that suppurative pericarditis had developed. The x-ray film, although it showed a large pericardial shadow, was confusing because the opaque area extended far out into the left side of the chest. Paracentesis of the left pleural cavity revealed a pocket of pus in close relationship with the pericardium.

The pericardium was exposed and opened through a chondroxiphoid approach. It contained a large amount of thick pus and a number of adhesions between the layers of the pericardium. There was, also, a walled-off empyema between the left side of the pericardium and the lung just below the hilus and well down on the diaphragm. This was also drained.

The man was in very poor condition when operated on. He had a very low blood pressure and a rapid pulse rate. He died twelve hours after the operation.

Autopsy revealed a chronic empyemic cavity with much thickened walls which were in contact with the left side of the pericardium. We believe that he had the empyema first and that pyopericardium developed later as a complication of the suppurative pleuritis.

CASE 4.—A colored woman, 20 years of age, was operated on at the Baltimore City Hospitals, June 18, 1932, for pyopericardium. She had been ill with pneumonia since May 10. She was short of breath and had a paradoxical pulse; the roentgenogram disclosed a triangular pericardial shadow with the base below and the apex above.

At operation suppurative pericarditis was found. A moderate amount of thick creamy pus was evacuated. Cultures showed growth of a pneumococcus. The operative approach was by the chondroxiphoid route. The woman lived only a few hours after the operation.

CASE 5.—A white man, aged 29 years, was admitted to the hospital, May 22, 1933, with frank pneumonia, type IV, of the right lower lobe of two days' duration. On June 13, a thoracotomy was done for a localized empyema situated high up in the right side of the chest. On culture the fluid from this abscess yielded the pneumococcus. He had an enlarged pericardial shadow, and there was a friction rub in the cardiac area.

These findings, along with an enlargement of the cardiac area, cyanosis, pain in the epigastrium, a slightly paradoxical pulse, a temperature that ranged between 98 and 102 F., a blood pressure of 100 systolic and 60 diastolic, indistinct heart sounds and a white blood cell count of 23,050, indicated that he had the same sort of infection in the pericardium.

Accordingly, four days later, June 17, a pericardiotomy was done under 0.5 per cent procaine hydrochloride anesthesia. An oblique incision was made, extending from about the midline of the sternum downward and outward, parallel to and just above the costal margin. By means of a bur, an opening was made through the sternum over the triangle of safety. With a rongeur the hole in the bone was enlarged to the left, and the bridge of sternum and an inch (2.5 cm.) of the left fifth and sixth costal cartilages were bitten away. The vent exposed a taut pericardium. The surface of the heart lay close to the pericardium. On opening the pericardium, 2 ounces (59 cc.) of a murky serohemorrhagic fluid welled out

of the wound. The incision was made large enough to admit a finger. The surface of the heart was covered with a shaggy and patchy exudate. The pericardial sac was drained with two small rubber tubes. Irrigations were employed for a considerable period. The patient eventually made a satisfactory recovery.

*Comment.*—This is the only case in the series of 15 cases reported by us in which a patient with combined empyema and purulent pericarditis recovered. Three of the 5 deaths in the series were associated with the combination of empyema and suppurative pericarditis.

#### REVIEW OF NINETY-NINE CASES

In the present study, we tender an analysis of 99 extra cases<sup>3</sup> in which open drainage has been practiced for the relief of suppurative pericarditis. Ninety-four of these cases have been assembled from the literature. The observations listed in the foregoing pages constitute the remainder of the group. For the most part, these cases have been registered since April 30, 1927, and all of them during the present century.

*Sex and Age of Patients.*—Fifty-two of the patients were males and 21 were females—a ratio of males to females of  $2\frac{1}{2} : 1$ . Twenty-nine of the former, or 58.82 per cent, and 14 of the latter, or 66.67 per cent, recovered. Of the 26 patients whose sex was not recorded, only 6 or 11.54 per cent, recovered. While it is unsafe to make deductions from small series, the figures seem to indicate that the female is the better risk. Nineteen of the 99 patients were between 1 and 10 years of age; 18 between 10 and 20; 19 between 20 and 30; 4 between 30 and 40; 4 between 40 and 50; 2 between 50 and 60, and 1 between 60 and 70. The remainder were designated as men, women or children or were not designated with regard to sex or age. Of the 67 patients whose ages were recorded, 56 were under 30 years of age and 30 were less than 20 years old. Only 11 were over 30 years of age. Thus a large majority of these patients were under 30 years of age and a goodly proportion of them were less than 20 years old. The disease is therefore preeminently one of youth.

*Etiology.*—In 8 cases the pericarditis was caused by direct implantation of pyogenic organisms introduced from without by bullet or by knife wounds. In 27 cases no mention was made of the source of the infection. In 1 instance, nothing was found to account for the condition. This, however, could hardly have been an example of the idiopathic variety of purulent pericarditis described by some authors, because

3. Three cases attributed to L. E. Vasquez are not included here because the abstract of his article entitled "Suppurative Pericarditis Complicating Bronchopneumopulmonary Diseases" (J. A. M. A. 98:1042 [March 19] 1932) is lacking in data, and the original paper published in *Salvador Médico*, San Salvador (10:6, 1931), could not be secured.

autopsy revealed a fistulous connection between the pericardium and the left bronchus. In the majority of instances, the pyopericardium was attributed to a metastasis from a distant focus of infection. Osteomyelitis and suppurative processes in other tissues were responsible for 13 of these cases, and diseases of the respiratory tract accounted for 49. Of great interest, in this connection, was the incidence of

TABLE 1.—*Etiology of Pericardial Effusion*

	Recovered	Died	Not Stated	Total
Pneumonia .....	12	7	0	19
Pneumonia (streptococci), pleurisy.....	1	0	0	1
Pneumonia, empyema .....	5	2	0	7
Pneumonia, empyema, pleurisy.....	2	1	0	3
Pneumonia (streptococci), empyema (bilateral) consecutive to thyroidectomy.....	0	1	0	1
Pneumonia, empyema, suppurative otitis media.....	1	0	0	1
Pneumonia, pleurisy .....	0	1	0	1
Pneumonia, abscess of shoulder.....	1	0	0	1
Pneumonia, infection of upper respiratory tract, otitis media.....	0	1	0	1
Pneumonia, empyema consecutive to grip.....	0	1	0	1
Pneumonia, osteomyelitis consecutive to grip.....	1	0	0	1
Bronchopneumonia, empyema, osteomyelitis, endocarditis consecutive to tonsillitis.....	1	0	0	1
Bronchopneumonia consecutive to osteomyelitis.....	1	0	0	1
Empyema (bilateral) .....	0	1	0	1
Empyema .....	0	1	0	1
Empyema, osteomyelitis .....	0	1	0	1
Pleurisy following otorrhea.....	0	1	0	1
Pleurisy following osteomyelitis.....	1	0	0	1
Tonsillitis .....	2	1	0	3
Tonsillitis (streptococci) .....	0	1	0	1
Tonsillitis, osteomyelitis .....	1	0	0	1
Osteomyelitis .....	1	1	0	2
Chondral abscess .....	1	0	0	1
Otitis media, jugular thrombophlebitis.....	1	0	0	1
Abortion, septicemia .....	0	1	0	1
Pyemia .....	0	1	0	1
Abscess of nates.....	1	0	0	1
Infection of arm.....	1	0	0	1
Erysipelas of face.....	1	0	0	1
Scarlet fever .....	1	1	0	2
Extraction of tooth.....	1	0	0	1
Actinomyces .....	0	1	0	1
Epithelioma of lip, with dissection of submaxillary triangles.....	0	1	0	1
Gunshot and stab wounds.....	5	1	0	6
Gunshot wound and actinomyces.....	0	1	0	1
Wounded by piece of metal.....	1	0	0	1
None found .....	0	1	0	1
Not given .....	6	17	4	27
Totals.....	49	46	4	99

pneumonia and empyema, either alone or in combination, as a coincidental, primary or secondary process, one or both being noted 42 times. When pneumonia and empyema were both present, the former, as a rule, antedated the latter. Twice, the empyema was overlooked and was discovered first at autopsy. Empyema in association with suppurative pericarditis is a serious combination. Of our 12 patients, 4 had empyema, and of the lot only 1 patient recovered. In 22 of the 99 cases constituting this series empyema was recognized and was drained, with 13, or 59.09 per cent, recoveries and 9, or 40.91 per cent, deaths.

*Bacteriologic Examination.*—Bacteriologic examination of the pus was made in 53 of the cases. In 5 instances, the culture was sterile. The exudate was thrown away by mistake in another instance. While scattered other organisms were mentioned, the chief offenders were the pneumococcus, 21 times, or 39.62 per cent; the staphylococcus, 12 times, or 22.64 per cent, and the streptococcus, 12 times, or 22.64 per cent. Death occurred in 38.09 per cent of the purulent pneumococcic group; in 25 per cent of the staphylococcic, and in 50 per cent of the streptococcic group. It is not safe to generalize, however, from such a small series. In our first series, the death rate in the pneumococcic

TABLE 2.—Results of Bacteriologic Examination

	Recovered	Died	Not Stated	Total
Pneumococcus .....	21	6	0	27
Pneumococcus, type I .....	0	1	0	1
Pneumococcus, type I and gram-positive cocci.....	1	0	0	1
Pneumococcus, type II .....	1	0	0	1
Pneumococcus, type IV .....	0	1	0	1
Staphylococcus .....	2	2	0	4
Staph. pyogenes-aureus .....	4	1	0	5
Staph. pyogenes-aureus-haemolyticus .....	1	0	0	1
Staph. pyogenes-albus .....	1	0	0	1
Staph. pyogenes-aureus and gram-positive bacillus.....	1	0	0	1
Streptococcus .....	1	1	0	2
Str. nonhaemolyticus .....	1	0	0	1
Str. haemolyticus .....	1	4	0	5
Str. haemolyticus, Bacillus mucosus-capsulatus and a gas-forming anaerobe .....	0	1	0	1
Str. haemolyticus, gram-negative and gram-positive cocci in short chains.....	1	0	0	1
Str. haemolyticus and gram-positive bacillus.....	1	0	0	1
Str. later, at first gram-positive bacillus and cocci.....	1	0	0	1
Bacillus influenzae .....	0	1	0	1
Diverse organisms .....	1	0	0	1
Unidentified organisms .....	0	1	0	1
Culture sterile .....	3	2	0	5
Pus thrown away by mistake.....	0	1	0	1
Not stated .....	17	24	4	45
Totals.....	49	46	4	99

group was 37.03 per cent; in the staphylococcic, 53.8 per cent, and in the streptococcic, 30.8 per cent. These figures give for the two series about the same percentage of deaths in the pneumococcic type, but the mortality rate in the streptococcic and staphylococcic types is reversed.

*Diagnostic Puncture.*—Diagnostic aspiration is valuable only when fluid is obtained, but it should also be remembered that pericardiocentesis, even in the presence of pus, may yield a dry tap (Massart and Béchet, Goinard). For this reason it may prove a hindrance rather than an asset. Such an experience by tending to upset an otherwise well established diagnosis made Coutts momentarily hesitate about sanctioning operative relief. Many authorities, however, unequivocally condemn the use of the aspirating needle on the grounds (1) that it is too hazardous and (2) that it is unnecessary for the making of a correct

diagnosis in the presence of the characteristic physical signs and roentgenographic evidence. If in doubt as to the nature of the disease, it is much safer, they claim, to cut down onto the pericardium and to enter this structure under direct vision rather than to insert a needle blindly into the chest with the possibility of entering the pleural cavity and thus instituting an empyema or of puncturing the heart and causing hemorrhage. Fortunately the latter accident is relatively rare, and, if it does occur, it is ordinarily quite innocuous. When paracentesis pericardii has been definitely decided on, Pincoffs advises that the needle should be introduced close to the sternum through the lowest possible intercostal space on the left side, with its point directed slightly downward and laterally so as to parallel the ventricles. In this connection, the situation of the heart, when the pericardium is more or less full of fluid, is of some moment. Bréntano declares that in all pericardial effusions the heart lies most often right against the anterior wall of the sac even if adhesions are not present, and that in many cases there will be a fusion between the pericardium and the anterior wall of the heart. This means that the heart is liable to be punctured unless great care is exercised on the introduction of the needle. In all of our cases the exudate had pushed the heart forward, where it lay in juxtaposition to the pericardium.

In this series diagnostic puncture was practiced on 47 patients without injury to any vital structure. In contrast, however, to these figures, West and others have reported this accident. In view of these adverse experiences we feel that the procedure is contraindicated, especially as it is not necessary for localization as in thoracentesis. No aspiration was done in 7 cases, including our 5 observations. In 45 instances the report failed to mention whether the procedure was or was not employed. To avoid the hazards attendant on aspiration, slight as they appear to be, we prefer to expose the pericardial sac rather than to run the chance of injury to the heart, the pleura, the intercostal vessels, the coronary vessels or the peritoneum.

*Pus.*—In the large proportion of cases, the pus had collected behind the heart and had pushed this organ forward directly against the anterior pericardial wall. In a few instances, the heart was attached to the pericardial sac by firm adhesions. Usually it was closely approximated to the pericardium, but, on rare occasions, a thin layer of pus was interposed between these structures. Accordingly, paracentesis is inadvisable, as there is considerable danger of injuring the heart. The amount of pus recovered varied from a few drachms to as much as 2,500 cc. Often the exudate was under high pressure. It was described as foul, yellow, turbid, serohemorrhagic, sanguinopurulent, blood-tinged, thick, fetid, thin, cloudy, creamy, chocolate, liquid, greenish, murky, yellowish green. While in case 5 of our present series, the



fluid evacuated was not actually purulent, it was potentially purulent, for it contained a pyogenic organism, the pneumococcus, and the discharge promptly changed to pus soon after free drainage had been established. Other observers have had the same experience.

In this connection, it is well to remember that it is not the amount of pus that causes the embarrassment to the circulation, but the rapidity with which the effusion occurs. The auricles will tolerate a degree of pressure from a slowly increasing exudate that they could not withstand from a rapidly accumulating effusion. It is in the latter group that prophylactic aspiration has a field of usefulness by releasing the pressure on the auricles and by keeping the patient alive until such time as his condition will warrant the institution of more radical measures.

*Symptomatology.*—The signs and symptoms are inconstant with a few exceptions. One would expect the heart sounds to be indistinct, and many reports state this as a fact, but the apex of the heart is usually found lying against the anterior layer of the pericardium, and this may give a misleading clearness and nearness to the sounds of the heart. The pulse is usually quickened and the heart action weakened. The few records of blood pressure that are reported show that the pressures were low. Shortness of breath and cyanosis are commonly present. A pericardial friction rub is a fleeting and uncertain sign owing to the fact that the pericardial surfaces are seldom in contact. The paradoxical pulse is fairly constant, but it is not always present. Bulging between the cartilages may be observed in children when there is a large effusion, but this sign is not often encountered. The usual symptoms of sepsis are always present to a varying extent—fever, sweating, exhaustion, leukocytosis.

The outstanding symptoms are those of a septic process associated with cardiac distress and shortness of breath, alterations in the quality of the heart sounds and enlargement in the area of cardiac dullness. In clinching the diagnosis, the most useful confirmatory help is the x-ray film. Ordinarily the shadow of the heart is triangular with the base up, and the outline of the heart is quite clearcut. The apex is seen to the left of the sternum, and the shadow of the apex is rather narrow. In pyopericardium there is a broadening of the pericardial shadow downward. If the effusion is abundant, the shadow is distinctly characteristic and is spoken of as bottle-shaped; but, if the amount of pus is small, the x-ray film may not be so helpful.

*Diagnosis.*—Inasmuch as the symptoms are inconstant, a correct diagnosis depends largely on the recognition of those diseases of which pyopericardium is a complication. When a patient suffering with empyema, abscess of the lung, osteomyelitis or suppurations within the abdomen continues to be ill after the institution of adequate drainage.

purulent pericarditis is one of the complications that should not be overlooked. Then with a careful routine examination of the chest, supplemented by a roentgenologic study and, if necessary, by a paracentesis pericardii, no great difficulty should be experienced in arriving at a proper conclusion.

In this series of 99 cases, the diagnosis was made before operation in 64 instances; in 3, after opening the chest for the evacuation of a supposed empyema; in 1, by accident, after the resection of a diseased costal cartilage. In 1 case, on entering the pleural cavity, a knife blade was found to have penetrated and to have infected the pericardium. In 30 instances the time of the diagnosis was not mentioned.

*Primary Operative Results.*—Of the 99 patients, 49, or 49.49 per cent, recovered; 46, or 46.47 per cent died. In 4 cases, or 4.04 per cent, the outcome was not mentioned.

According to Rhodes, the death rate in patients not operated on or treated by therapeutic aspiration is 100 per cent. On comparison of these figures, the superiority of pericardiotomy is indisputable in that it offers a salvage of 50 per cent against, at best, only sporadic cures by other kinds of treatment.

A resection of a costal cartilage or of a rib was done in 43 cases; 24, or 55.81 per cent, of the patients recovered, and 19, or 44.19 per cent, died. According to the individual preference of the surgeon, the costal cartilages from the third to the seventh rib on the left side and from the fourth to the fifth on the right side were selected for this purpose, but the left fifth and sixth ribs were the ones most often excised.

In this series, an intercostal space was not used as an avenue of approach to the pericardium in a single instance. In the remaining 56 cases, the operation was performed by the transsternal route 3 times, with 2 cures and 1 death; once by a posterior approach, with death; once by the trap-door method, with cure; once by the "usual operation," with cure; thrice the condition was discovered by accident, with 2 cures and 1 death; 6 times by the insertion of a trocar and by the institution of continuous drainage, with 1 cure and 5 deaths; on 14 occasions by the epigastric route either with or without resection of one or more costal cartilages, with 8 recoveries and 6 deaths. In 21 operations which were not described, 6, or 28.57 per cent, of the patients recovered; 11, or 52.38 per cent, died. In 4 cases, or 19.05 per cent, the result was not given. In 6 cases, 2 operations were necessary, with 4 recoveries and 2 deaths (Bransfield, Hilse, Loucks, Sherwood, Truesdale, Heuer).

Truesdale favors the extreme lateral and most dependent area of the pericardium as the point of election for drainage. In the second

of his 2 cases he employed this procedure after having failed to evacuate the pus satisfactorily by a resection of the left fourth and fifth costal cartilages. In this instance, the pericardium was adherent to the pleura, which permitted the sac to be drained without the pleural cavity being traversed. Certainly, such favorable conditions would not ordinarily prevail. On the whole, we feel that the best approach for the operative relief of purulent pericarditis is the costoxiphoid route with resection of the left seventh, sixth and fifth costal cartilages together with a portion of the sternum, if this is found necessary. At any rate by affording more room, this procedure adds greatly to the comfort of the surgeon and lessens rather than increases the operative hazards.

The probability of the patient's recovery, however, seems to depend more on the etiology of the lesion than on the method by which the pericardium is attacked. There were 8 cases of gunshot or stab wounds, with cures in 75 per cent (one of the deaths, that in case 44, cannot rightly be attributed to the pyopericardium, which had healed when an actinomycosis developed elsewhere from which the patient eventually died; the other death, that in case 45, was the result of exsanguination from repeated small hemorrhages); 49 cases of respiratory lesions with cures in 59.18 per cent, included in this group, were: 39 cases of pneumonia, with cures in 64.10 per cent; 1 of pyemia, with a fatal outcome, and 8 in the osteomyelitic group, with cures in 25 per cent.

Open drainage at the earliest possible moment appears to be the best way of handling this malady. Unfortunately, a careful analysis of the available material is not in accordance with this view, for of the 55 patients operated on from a few days to four weeks after the onset of symptoms, 37, or 67.28 per cent, recovered and 18, or 32.72 per cent, died; of 39 patients operated on within five days, 24, or 61.54 per cent, recovered and 15, or 38.46 per cent, died; of 16 patients operated on after five days, 13, or 81.25 per cent, recovered and 3, or 18.75 per cent, died. In spite of these figures we feel that early operation is the better plan to follow, because pus on general principles should be evacuated at the earliest possible moment.

In this connection, Klose and Strauss voice the opinion that it is best to operate before the exudate has changed to pus. They claim that suppurative pericarditis may be prevented, even in the presence of pyogenic organisms, if such a policy is adopted, and they furnish as substantiatory evidence the report of a case in which they operated in this stage with success. Both our experience and that of Brooke seem to support this contention. Brooke claims to have cured 2 patients by pursuing this policy. In case 7 of our first series, the fluid was hemorrhagic and the patient recovered satisfactorily. In case 82 of our second series, the exudate was a murky hemorrhagic fluid which contained

in culture type IV pneumococci. This patient also recovered. Here, then, are 5 cases in which the effusion was infected but nonpurulent and in which all of the patients recovered. The question naturally arises, should this be the line of treatment invariably pursued in cases of exudative pericarditis potentially purulent? The evidence seems to warrant such a policy, but the answer must await further confirmation. These are desperate cases, and anything that holds the promise of a definite lessening in the mortality rate should be given an extended trial.

Our investigations lead us to believe that if the patient is in bad shape, a reasonable delay in the institution of pericardiotomy does not materially compromise his chances for recovery.

When the disease has become fully established, it appears that the only hope for lowering the mortality rate is the early recognition and the prompt evacuation of attendant purulent foci. No matter how well or at what stage pericardiotomy is performed, it fails to succor if an abscess in the pleural cavity is overlooked, or if secondary collection of pus in the pericardial sac escapes detection. Occasionally a secondary intervention may be found necessary to relieve a pocketing of the pus, for better drainage, or to prevent blockage of the drainage tube. Among the 99 instances herein collected, this happened 3 times, namely, once each in cases reported by Hilse, Loucks and Truesdale, with 2 recoveries and 1 death. If the avenue of approach does not permit proper drainage of the pus, another route may have to be adopted. For example, Bransfield, after the resection of the left fourth costal cartilage with the recovery of only 1 ounce (about 29 cc.) of pus, suspected that the pericardial sac had not been thoroughly emptied. He thereupon excised the left fifth and sixth costal cartilages with the release of one-half pint (about 236 cc.) of fluid and cured his patient. Heuer on resection of the left fifth costal cartilage found the heart in direct contact with the pericardium and adherent to it. Efforts to free these structures had to be stopped because of damage to the cardiac musculature. Heuer turned the patient on his side and excised a rib in the posterior axillary line so as to permit an approach to the pericardium from behind. The lung was found to be adherent to the parietal pleura. Accordingly a needle was thrust through the lung into the pericardial sac, and thin pus was withdrawn. The lung was, therefore, penetrated with a blunt instrument, and tube drainage was instituted. The patient was cured of his pyopericarditis, but died six months later of an actinomycosis of the dorsolumbar region. Sherwood by accident entered the pleural cavity. He met the situation by the insertion of a gauze pack into the wound. Two days later he opened the pericardium with a cautery, and cured his patient. Miller resected the fifth costal cartilage, inserted a gauze pack, and twenty-four hours later incised the pericardium, with

recovery of the patient. Adye-Curran and Buernmann released the contents of a postoperative encysted abscess by puncturing the wall of the pocketed pus with a finger introduced through the original wound.

On occasion, the heart has been noticed to cease beating when the pericardium was incised. This peculiar phenomenon, spoken of as cardiac "standstill," occurred in cases reported by Harrigan, Metivet, and Ljunggren. In Harrigan's case, the temporary arrest of the heart was relieved by the placing of the drains. Metivet had a strikingly similar experience. With the injection of epinephrine hydrochloride into the cardiac musculature, pulsation returned, but ceased permanently in half an hour. Ljunggren also reported a heart block which behaved precisely like those in the preceding two cases. The heart lay motionless in its sac, but on compression of the left ventricle it began to pulsate again.

On rare occasion the pericardial effusion has been evacuated through the left pleural cavity. In most of these cases a thoracotomy had been performed for a supposed pleural exudate, but a distended pericardium was found to exist instead and was drained through the original wound (Colwick, Magie). West, Savory, Lane and Steward and Garrod have also recorded cases illustrative of this mistake. Cochez and Fenouillet, after the resection of a diseased cartilage and rib, saw pus issuing from a vent in the bed of the operative field. While performing débridement of this area, they discovered that the fistula pierced the pericardium.

While the closed method of emptying pus from the pericardial cavity, as devised, described and practiced successfully by Whittemore, may not come strictly under the head of pericardiotomy, it is nevertheless akin to that procedure in that the surgeon exposes the pericardium through an open incision before he punctures the wall of the pericardium with the trocar. This procedure is applicable, however, only before large masses of fibrin have formed; otherwise some one of the open operations must be employed.

In the present series, the closed type of drainage was practiced 7 times, with cure in 1, or 14.29 per cent of the cases, and death in 6, or 85.71 per cent. While the number of cases is too small to serve as the basis of accurate conclusions, the results are quite suggestive, i. e., 14 per cent of the patients were cured by the closed method of drainage as against 55 per cent cured after the resection of a costal cartilage and open evacuation of the pus. It appears from these figures that closed drainage has no place in the treatment of purulent pericarditis.

Empyema developed in 24 of the 99 patients some time during the course of their illness. Whether the suppurative pleuritis occurred primary to, simultaneous with, or subsequent to, the pyopericardium, the combination was a bad one and proved a distinct handicap to the victim's

chances of recovery. Twice the empyema was not discovered until autopsy. In the remaining 22 cases, the condition was recognized clinically and the pus drained off, with 13 recoveries and 9 deaths (4 of the patients were from the University of Maryland Clinic; 1 recovered and 3 died).

In the 22 cases in which operation was resorted to, the empyema involved the left side 12 times, with 7, or 58.33 per cent, recoveries, and 5, or 41.67 per cent, deaths; the right side 7 times, with 6, or 85.71 per cent cures and 1, or 14.29 per cent, deaths; in 2 cases the disease was bilateral, with no recoveries, and in 1 case with a fatal issue, the affected side was not recorded (table 3). These figures seem to indicate not only that a left-sided empyema is more prone to be followed by suppurative pericarditis but that the combination is much more serious than a right-sided empyema and purulent pericarditis.

Pleurisy with effusion developed in 7 patients; 6 of these patients recovered and 1 died.

*Secondary Operative Results.*—Operative intervention for pyopericardium has been condemned as unwarranted on the ground that if the patient escapes with his life, he will sooner or later succumb to obliterative pericarditis. In such cases, death is delayed but not stayed, and life is prolonged only for a shorter or longer period at the expense of a crippling invalidism, unless the patient is relieved by cardiolysis, a procedure as yet of too recent development to have established its actual value. Fortunately 39 cases are available in this and our first series which throw considerable light on this phase of the subject. Instead of supporting the commonly accepted opinion that a fatal adhesive pericarditis is an inevitable consequence, these cases supply ample proof to the contrary. In all of these cases, at least one year had elapsed since the pericardiotomy, and in one instance as long as thirty-two years (Porter's) and in another (Lilienthal's) twenty-one years had supervened. Thirty-five of these patients were alive, well and at their usual vocations at the time of the report, with their cardiac boundaries within normal limits. One was still alive, but had adhesive pericarditis, and his death was momentarily expected (Davis). Of the 3 remaining patients, 1 had died three years after the pericardiotomy, but the cause of death was not known (Eiselsberg); 1 had died of an abscess of the brain a year later (Johnson), and 1 of an adhesive pericarditis (Darrach).

Thus only 2, or 5.13 per cent, of these 39 patients had acquired intrapericardial adhesions to such degree as to cause baneful symptoms. In the light of these observations, it appears that the occurrence of mortal adhesive pericarditis is exceptional and not as common as heretofore supposed.

We have little doubt that other cases might have come in this category had the patient lived or had not the adhesions been destroyed either at the time of operation or at that of a secondary intervention. For instance, in case 6 of our first series, it was necessary a few days after the pericardiotomy to insert a finger into the wound. Some pocketed pus and a few loose adhesions were detected, and the adhesions were broken up. Eight years later, the patient was well and did not show any evidence clinically of impaired cardiac action. It is too soon, however, to predict the ultimate result, but from present appearances the child is completely cured. Pool had a similar experience, but his patient died thirteen days after the pericardiotomy. In case 7 of our first series, some firm, dense adhesions were found sealing the heart to the pericardium anteriorly at the operation. This patient had a stormy convalescence. Seven years have now elapsed without clinical evidence of any damage to the heart. Delorme, Sievers, Stoker and Allingham found extensive adhesive pericarditis in their cases at autopsy, but none of the patients had survived operation as long as a month.

*Drainage.*—More than half of the operators showed a preference for tube drainage. Usually two tubes were employed, in which case one was placed in the culdesac on each side of the heart. Next in popularity came rubber tissue. In 1 case the wound was left open, and no artificial drainage was used. The pericardium was sutured to the skin or to the subcutaneous tissues and a tube or gauze put down to but not into the pericardial sac on 9 occasions. When the pericardium was stitched to the muscles or to the skin, a slightly longer time elapsed before complete closure of the wound than in those cases in which the pericardium was treated otherwise. On the whole, there is not much choice between the methods practiced. All are attended by about the same percentage of primary recoveries.

Lindner, Lane and Lilienthal had to discontinue tube drainage, however, because the tube impinged on the heart and by irritating it caused a stormy and irregular cardiac action. Riedel and Eichel, in pericardiotomies performed for conditions other than purulent pericarditis, noticed the same phenomenon.

In Underhill's case, a sharp hemorrhage occurred from the drainage tube two days after the pericardiotomy. This was repeated at intervals until the death of the patient.

*Irrigation.*—Irrigation was used in 37 cases. Twenty of the patients recovered, 16 died, and in 1 case the result was not mentioned. The solutions used were: acriflavine, an acid solution of hypochlorite (eusol), surgical solution of chlorinated soda, physiologic solution of sodium chloride, hydrogen dioxide, mercurochrome, a flavine dye and quinamil. In 59 instances, no mention was made of irrigation; of the patients, 26

recovered and 30 died. The results in 3 cases were not recorded. In 3 cases it is specifically stated that irrigation was not employed; all of the patients recovered.

It appears from these figures that in most instances irrigation had but a slight influence on the result. We feel that the question of whether to irrigate or not to irrigate depends largely on the character and on the amount of the exudate and on the condition of the patient. We have found this a good rule to follow: If the patient is doing well, leave him alone.

If irrigation is employed, provision must be made, without fail, for the return flow of the irrigating fluid. This means the insertion of two tubes into the pericardial sac. Parker's experience illustrates well the penalty for failure to realize the importance of this precaution. In his case, the pus did not flow well after the pericardiotomy. It was thick and contained membranous shreds. Irrigation was practiced, but the opening in the pericardium became plugged with lymph, and the pressure of the trapped fluid on the heart proved fatal. Rhodes had a similar experience. While he was washing out the pericardium, the catheter became plugged. The patient grew cyanotic, gave a few convulsive jerks and apparently was dead. The catheter was pulled out. This was followed by a gush of irrigating fluid. Respirations began immediately and the patient appeared to be as well as ever, but he died several days later. In Brown's cases, also, the irrigating fluid was trapped, with the occurrence of "Herzdruck," which was promptly relieved on the escape of the fluid.

Among others, Brown, Bransfield, Sherwood and White used surgical solution of chlorinated soda with satisfaction. Its use by Cutter resulted in a marked arrhythmia. This irregularity was preceded by a distinct acceleration of the heart beat. Loucks had to discontinue its use because a bronchial fistula developed. Jopson used it with great trepidation and in fact had to discontinue its use because it was not tolerated.

*Prognosis.*—The prognosis, though always grave, is by no means hopeless. Even in apparently moribund patients, striking cures have occurred. In this series 18 patients were so listed, with 10 recoveries and 8 deaths. Of much significance from a prognostic standpoint is the etiologic element. Those cases caused by the introduction of pyogenic organisms directly from without on bullets or on knife blades, in which the disease is, therefore, limited to the pericardial sac, give the best percentage of recoveries. The pneumococcic variety yields in round numbers 50 per cent of the cures. The streptococcic and staphylococcic types have the least favorable prognosis.



When the pericarditis is an expression of a generalized septic process, the field for successful operative intervention seems to be small. Yet, limited as it is, it affords the sole chance of averting a fatal issue. On the other hand, practically all patients not operated on or treated only by aspiration die.

Complications necessarily fatal in themselves, unless detected early and promptly remedied, render the prognosis less favorable. Preemi-

TABLE 3.—*Pleural Complications: Empyema*

Case	Side	Operated On	Discovered at Autopsy	Recovered	Died	Comment
5	Left	Yes	....	....	Yes	
12	Left	Yes	....	Yes	....	Closed drainage
17	Left	Yes	....	....	Yes	Closed drainage
22	Left	Yes	....	Yes	....	Right-side fluid aspirated
23	Right	Yes	....	Yes	....	Aspirated
25	Left	Yes	....	Yes	....	
40	Right	Yes	....	Yes	....	
42	Bilateral	Yes	....	....	Yes	Closed drainage
43	Bilateral	Yes	....	....	Yes	Hemorrhage into pleural cavity
46	Right	....	Yes	....	Yes	
47	Left	Yes	....	....	Yes	
55	Left	Yes	....	Yes	....	
59	Left	Yes	....	....	Yes	
68	Right	Yes	....	Yes	....	
71	Left	Yes	....	Yes	....	
72	Right	Yes	....	Yes	....	
77	Right	Yes	....	Yes	....	Two aspirations
79	Left	Yes	....	....	Yes	
82	Right	Yes	....	Yes	....	
84	Left	Yes	....	Yes	....	
85	.....	Yes	....	....	Yes	Entered with empyema
88	.....	....	Yes	....	Yes	Pyopneumothorax
89	Right	Yes	....	....	Yes	
97	Left	Yes	....	Yes	....	
24	.....	22	2	13	11	
Pleurisy Tapped, Times						
2	.....	....	....	Yes	....	
3	Left	....	....	Yes	....	
20	Right	4	....	Yes	....	
35	Left	....	....	....	Yes	Of a secondary hemorrhage from internal mammary vein
58	.....	....	....	Yes	....	
65	.....	2	....	Yes	....	
67	.....	....	....	Yes	....	
7	.....	2	....	6	1	

ment among these is empyema. It was listed as having occurred 24 times. Twenty-two of the patients with empyema had the pus evacuated by thoracotomy, with 13 recoveries and 9 deaths. In 2 instances, the empyema was discovered at autopsy.

Occasionally, it has been found necessary to reopen the wound and to introduce the finger into the pericardial sac for the relief of secondary pockets of pus. While the mortality is high, cure has been effected even under such unfavorable circumstances.

In the general run of cases, the recovery rate is 51.58 per cent, or 1 of every 2 patients operated on. Much improvement in these results could be hoped for; but, when contrasted with the total collapse of other lines of treatment, these figures are a sufficient argument in favor of pericardiotomy for purulent pericarditis.

#### SUMMARY AND CONCLUSIONS

In closing we wish to stress the following points:

1. Purulent pericarditis is an abscess and, like a collection of pus anywhere else, should be treated by incision and adequate drainage.
2. Too much cannot be said in favor of early operation, but it should be remembered that late operation does not rob the patient of the hope of cure.
3. Operative treatment should yield a cure in 50 per cent of the cases.
4. The best approach is the costoxiphoid route with resection of the left seventh, sixth and fifth costal cartilages together with a portion of the sternum, when more room is needed.
5. Therapeutic aspiration may be used, on occasion, with profit, but it has no curative value.
6. There are three chief factors that govern prognosis: (1) the time of the operation; (2) the type of the organism, and (3) the original condition of which the pyopericardium is a complication.
7. Purulent foci elsewhere, unless detected early and promptly remedied, render the prognosis less favorable.
8. In the past seven years, there has been no appreciable improvement in the operative mortality rate.
9. Pyopericardium is a disease of youth. Eighty-three per cent of the patients are under 30 years of age.
10. Seventy per cent of the patients have been males, and 30 per cent have been females.
11. Troublesome postoperative adhesive pericarditis does not occur as often as it is generally supposed to do.

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# EFFECT OF CARBON ARC RADIATION ON HEALING OF BONE

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The remarkable advances made during the past decade demonstrating the rôle of ultraviolet energy in metabolism, the activation of inert substances and the relationship between ultraviolet rays and vitamin D have fired the enthusiasm of the public and furnished a fertile field for the researches of today and tomorrow. As in the case of many other scientific discoveries, however, commercialism and quackery, by incessantly instructing the laity that radiation, either by way of artificial sources or by the consumption of irradiated products, will cure all ills, have built up a false conception of its real value. To be unduly optimistic concerning the value of radiant energy in the treatment of disease, employing it to the exclusion of a hygienic-dietary régime, and to regard light as a *therapia magna*, are bound to bring discouragement.<sup>1</sup> Sunlight or artificial radiant energy will not cure, it is not a specific form of treatment, and it should not be used without medical guidance and adequate equipment. Further, although radiation may give marked effects in cases of abnormal condition, it plays only a minor part in the daily life of normal persons, who can get along with little or no sunlight provided the diet is adequate.<sup>2</sup>

However, notwithstanding these intimated exaggerations, radiation and irradiated materials have, in the proper hands, brought about some phenomenal results. Among the more outstanding are the effects on serum calcium and inorganic phosphorus in the healing of rickets and osteomalacia. Following these outstanding effects on abnormal mineral metabolism, it was logical to study the problem of fractures. Here there are two wholly contrasting views of the value of the results obtained. On the one hand, one reads: "From what has already been

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The data reported here were taken from the dissertation presented to the Faculty of the Graduate School of Tulane University in candidacy for the degree of Doctor of Philosophy by H. Morrow Sweeney in June 1934.

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2. Laurens, H.: Some of the Physiological Effects of Radiant Energy, J. Optic Soc. America **18**:237, 1929.

said about the effects of radiation on phosphorus and calcium metabolism, it might be expected that ultraviolet radiation would be of benefit in cases of ununited fractures, and this is amply borne out by clinical experience. As soon as it has been decided that there is delayed union, radiation should be given, as in this way not only are the reparative processes stimulated and the union of the fragments hastened, but there is a better functional result";<sup>3</sup> or, "there is no correlation between calcium and phosphorus determinations and fractures";<sup>4</sup> again, "ultraviolet radiation does not influence the union of fractures."<sup>5</sup> These and other statements illustrating differences of opinion in this matter stimulated us to carry out a fully controlled study of the subject by experimentally fracturing the fibulas of animals and then administering measured amounts of carbon arc radiation.

#### REVIEW OF THE LITERATURE

The vast amount that has been written on the effects of solar radiation, artificial radiation and irradiated materials fed by mouth precludes a systematic survey of it in this article. For this, one is referred to the reviews which have appeared, such as those of Clark,<sup>6</sup> Mayer,<sup>7</sup> Rollier<sup>8</sup> and Laurens.<sup>9</sup> In this article reference will be made only to facts pertinent to our own study.

Although it is repeatedly stated that light causes an increase in metabolism, this is not supported by experimental data, and there is adequate proof that higher mammals and man are able to endure long periods of darkness with no evident harmful effects, although metabolism may be somewhat lower in darkness than in light.<sup>2</sup>

Recent studies of rickets have given much evidence as to the action of sunlight, artificial radiation and irradiated materials in the metabolism of calcium and phosphorus. Raczynski,<sup>10</sup> in 1912, first showed the influence of sunlight on these constituents. Two puppies of the

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9. Laurens, H.: (a) *The Physiological Effects of Radiation*, Physiol. Rev. **8**:1, 1928; (b) *The Physiological Effects of Radiant Energy*, New York, The Chemical Catalog Company, Inc., 1933.

10. Raczynski, M. J.: *Recherches expérimentales sur le manque d'action du soleil comme cause du rachitisme*, Compt. rend. Assoc. internat. pédiat. **1**:308, 1912.

same litter were separated, one being kept in the sunlight and the other in darkness. Chemical examination of the bodies revealed that the body of the first puppy contained more calcium and phosphorus than that of the second. Powers and Park<sup>11</sup> definitely demonstrated that sunlight will stimulate a deficient calcium and phosphorus balance. A seasonal tide in the blood phosphates in infants was demonstrated by Hess and Lundagen,<sup>12</sup> and a similar tide in blood calcium in rabbits, by Grant and Gates,<sup>13</sup> the higher levels for calcium in March and December being accompanied by lower levels for phosphorus. Orr, Magee and Henderson<sup>14</sup> definitely demonstrated in pigs the effect of cod liver oil and radiant energy on the assimilation of calcium. When the oil was added to the diet or when the pigs were irradiated, the retention of calcium was raised from a minus quantity to over 60 per cent of the intake. Burton<sup>15</sup> demonstrated an increased retention of calcium and phosphorus in boys who were given a diet high in these minerals and who received ultraviolet radiation. Hess and Lewis<sup>16</sup> pointed out that viosterol increases the calcium and phosphorus not only in patients with rickets or tetany but in normal persons. The results of the complete metabolism studies of patients made by Bauer and Marble<sup>17</sup> present convincing evidence that viosterol increases the amount of calcium absorbed from the gastro-intestinal tract. If this increased absorption occurs at a time when the body needs calcium, there result an increased deposition of calcium and an increased number of trabeculae in the bones.

The numerous studies of the conditions governing the process of ossification have given rise to several theories to account for the phenomena observed. Many observers have used the calcium-phosphorus product as an index of the probable course of the healing process.

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11. Powers, G. F., and Park, E. A.: Prevention of Development of Rickets in Rats by Sunlight, *J. A. M. A.* **78**:159 (Jan. 21) 1922.

12. Hess, A. F., and Lundagen, M. A.: Seasonal Tide of Blood Phosphate in Infants, *Proc. Soc. Exper. Biol. & Med.* **19**:380, 1922.

13. Grant, J. G. B., and Gates, F. L.: Some Factors Affecting the Levels of the Serum Calcium and Phosphorus of Normal Rabbits, *Proc. Soc. Exper. Biol. & Med.* **22**:315, 1925.

14. Orr, J. B.; Magee, H. E., and Henderson, J. M.: The Effect of Irradiation with the Carbon Arc on Pigs on a Diet High in Phosphorus and Low in Calcium, *J. Physiol.* **59**:25, 1924.

15. Burton, H. B.: Influence of Cereals upon Retention of Calcium and Phosphorus in Children and Adults, *J. Biol. Chem.* **85**:405, 1930.

16. Hess, A. F., and Lewis, J. M.: Clinical Experience with Irradiated Ergosterol, *J. A. M. A.* **91**:783 (Sept. 15) 1928.

17. Bauer, W., and Marble, A.: Preliminary Note on Mode of Action of Irradiated Ergosterol, *New England J. Med.* **201**:809, 1929. Bauer, W.; Marble, A., and Claffin, D.: Studies on the Mode of Action of Irradiated Ergosterol, *J. Clin. Investigation* **11**:1, 1932.



There is diversity of opinion as to the validity of this product as an index, and there are differences in the figures found and proposed as indicative of union and nonunion. Tisdall and Harris,<sup>18</sup> in 1922, reported from clinical observation that certain definite and important changes in the inorganic metabolism invariably accompany repair of bone, namely, a slight increase in the serum calcium and a marked increase in the inorganic phosphorus. Their experimental work with dogs which had undergone artificial fracture and received radiation or irradiated materials gave no reliable results because of the impossibility of immobilizing the fragments.

Johnson<sup>19</sup> stated that nonunion other than that of mechanical origin can be definitely predicted if the product of the calcium and the inorganic phosphorus of the blood falls below 35 and is probable if it falls below 40. He stated the belief that it is improper to attempt to correct nonunion surgically, as is often done, until the causative factor, a low calcium-phosphorus product, is corrected by diet, cod liver oil or heliotherapy.

Petersen,<sup>20</sup> working on dogs with experimental fractures, fed diets containing adequate and inadequate calcium and phosphorus. When the animals were given a diet that markedly reduced the product and a fracture was made, nonunion invariably resulted. When the animals were again placed on adequate diets, resulting in a rise of the product to normal, healing took place. A product of 30 was found to be the figure of differentiation between union and nonunion. In a clinical study Petersen<sup>21</sup> found that in many cases of ununited fracture there was, as an underlying basis, a constitutional disturbance responsible for the condition, demonstrable as a deficiency in the inorganic bone-forming elements of the blood. Of the two elements, calcium and phosphorus, the latter was usually at a low level and at fault. In this type of case there was usually an abundant callus but no calcification, whereas patients with low serum calcium usually showed little or no callus. Petersen again noted that when the product of the inorganic constituents was below 30 there was no healing; when between 30 and 35 slight healing, and when above 35 active healing. In one case irradiation with ultraviolet rays from a quartz mercury vapor lamp was very effective.

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18. Tisdall, F. F., and Harris, R. I.: Calcium and Phosphorus Metabolism in Patients with Fractures, *J. A. M. A.* **79**:884 (Sept. 9) 1922.

19. Johnson, R. W.: The Healing Process in Fractures, *South. M. J.* **21**:394, 1928.

20. Petersen, H. A.: Study of Ununited Fractures with Especial Reference to Inorganic Bone-Forming Elements in the Blood Serum, *Bull. Johns Hopkins Hosp.* **35**:378, 1924.

21. Petersen, H. A.: A Clinical Study of Ununited Fractures with Special Reference to the Inorganic Bone-Forming Elements of the Blood, *J. Bone & Joint Surg.* **6**:885, 1924.

Ravdin and Jonas,<sup>22</sup> after studying a large group of normally healing and abnormally healing fractures, came to a conclusion similar to that of Petersen. They recognized that the absorption, excretion and utilization were not simple problems, but highly technical, and that the simple feeding of the salt in which the body was deficient was useless in many cases. Henderson, Noble and Sandiford<sup>23</sup> came to the following conclusions: The failure of a fracture to unite may be due to constitutional abnormalities, but while attempts to determine the abnormal constitutional variables should be made as a routine in addition to the use of surgical methods, the successful treatment of the average ununited fracture is in most cases a surgical problem.

Ravdin and Morrison,<sup>24</sup> in 1928, as a result of their observations, doubted that the product of the inorganic ions could be relied on as a prognostic index of the healing of a fracture. In a study of the serum calcium and inorganic phosphorus after fracture in normal, hypercalcemic and hypocalcemic dogs, they were unable to prophesy the rate of ossification from either the calcium-phosphorus product or the negative logarithm of the ionic product. Speed<sup>25</sup> also found the calcium-phosphorus ionic product unreliable for prognostic use in reference to his clinical observations. Estimations made on several hundred consecutive patients with fractures showed a normal range of serum calcium and inorganic phosphorus with products between 36 and 40. The fracture in some of these patients, however, went on to delayed union and nonunion. Throughout the treatment, the serum calcium content remained practically constant, while the inorganic phosphorus content varied, showing a regular sequence of events. Immediately after the fracture the inorganic phosphorus content was low, but within twenty-four hours it increased and remained high for a time, which seemed to vary with the period of disability, after which it returned slowly to normal. Increased muscular activity seemed to hasten its return, while diet had little or no effect. This change in ionic concentration was found to be about the same after other major operative procedures, except that in the major procedures the fall is more rapid. Speed produced experimental fractures in dogs: (a) during a period of a low phosphorus and a slightly lowered calcium content of the blood produced by a deficient diet; (b) during a period of high blood calcium content

22. Ravdin, I. S., and Jonas, L.: *Studies of Calcium and Phosphorus Metabolism in the Fracture of Bones*, *Ann. Surg.* **84**:37, 1926.

23. Henderson, M. S.; Noble, T. P., and Sandiford, K.: *Ununited Fractures with Special Reference to the Chemistry of the Blood*, *J. Bone & Joint Surg.* **8**:607, 1926.

24. Ravdin, I. S., and Morrison, M. E.: *Ossification After Fractures; An Experimental Study*, *Arch. Surg.* **17**:813 (Nov.) 1928.

25. Speed, K.: *Blood Serum Calcium in Relation to the Healing of Fractures*, *J. Bone & Joint Surg.* **13**:58, 1931.

produced by feeding large amounts of calcium lactate, and (c) during a period of low blood calcium content produced by parathyroidectomy, which brought about, in time, a high phosphorus content. As a result of this work, Speed stated the belief that determinations of the calcium and inorganic phosphorus content of the serum are valueless from a prognostic standpoint.

Peters,<sup>26</sup> in reviewing the whole topic of calcification, concluded that it cannot be correlated with the level of the serum calcium value. Even if the fraction of the serum calcium which depends on the protein content of the serum and apparently plays no part in calcification is disregarded, the calcium content is no criterion of the process.

Irradiation or the administration of vitamin D (viosterol) has been used by several investigators as a therapeutic measure, with widely varying results, in cases of fracture of the bone. Knoflach<sup>27</sup> treated patients with fracture of the long bones with viosterol and observed an increase in both the amount and the intensity of the callus in those who received the vitamin in contrast with those who did not. The increase began during the third week after fracture and was most prominent in elderly persons (over 55 years) and in children. Bors<sup>28</sup> administered viosterol to rats and rabbits having experimental fractures of the fibulas and reported an increase in both the amount and the calcification of the callus in those receiving the vitamin D product.

Lewis<sup>29</sup> studied the effect of viosterol on healing in seventeen cases of fracture of the long bones in adults. He was unable to observe any hastening of union or formation of callus. The values for calcium and inorganic phosphorus in the serum were not materially raised. Delayed union was present in six of the patients, and these, too, were not benefited. Cuthbertson<sup>30</sup> concluded that only in certain cases of pathologic fracture and abnormal bone metabolism does the addition of vitamin D to the diet appear to be of benefit. Indeed, the clinical after-history of some of his treated patients was that of delayed union.

By feeding viosterol in daily doses of 2 mg. or less, Grauer<sup>31</sup> observed a stimulation of the osteogenetic layer of the periosteum which

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26. Peters, J. P.: Chemistry and Physiology of Calcification, *Am. J. Surg.* **10**:530, 1930.

27. Knoflach, I. G.: Behandlung der Knochenbrüche mit bestrahltem Ergosterin, *Wien. klin. Wchnschr.* **4**:739, 1928.

28. Bors, E.: Vigantol und Fracturheilung, *Zentralbl. f. Chir.* **2**:3266, 1927.

29. Lewis, K. M.: Noneffect of Irradiated Ergosterol in the Treatment of Fracture, *Ann. Surg.* **92**:415, 1930.

30. Cuthbertson, D. P.: The Disturbance of Metabolism Produced by Bone and Nonbone Injury, with Notes on Certain Abnormal Conditions of Bone, *Biochem. J.* **24**:1244, 1930.

31. Grauer, R. C.: Effect of Viosterol on Periosteum in Experimental Fractures, *Arch. Surg.* **25**:1035 (Dec.) 1932.

resulted in a more rapid healing of experimental fractures in guinea-pigs. Greater doses caused retardation of the healing process, and huge doses (approximately 15 mg.) caused symptoms of osteitis fibrosa.

Swart,<sup>32</sup> experimenting on rabbits and rats, was unable to increase the rate of the healing of fractures or the amount of callus formed by administering viosterol by mouth in daily doses of 3 and 1.25 Gm., respectively. Murray<sup>4</sup> stated the belief that fractures always heal unless there is a mechanical bar to the growth of tissue and that healing is accomplished, as in other traumatized tissue, by the growth of granulation tissue derived from the adjacent traumatized soft parts, namely, the adjacent periosteum and endosteum and the alveolar tissue about the vessels in the marrow cavity and elsewhere. The source of calcium for this new-formed bone is dead, autolyzed bone at the site of fracture and not the blood stream. Vascular changes probably induce local changes in hydrogen ion concentration, which may influence the precipitation of calcium salts from solution or colloidal combination. Bone as a source of calcium can experimentally replace both inorganic and organic salts of calcium. Either precipitation or ferment-splitting activity may be responsible for the deposition of calcium, and the latter seems the more probable. Bone and the circulation through the soft parts are of prime importance in the process of calcification or healing of a fracture, and should therefore be prime objects of attention early in the process of bone healing. Oral administration of calcium and phosphorus and similar drugs is ineffective, and if calcium is needed in any person whose general calcium metabolism is normal, it must be supplied locally and not by way of the blood stream. Coulter and Smith<sup>6</sup> reported that in their experiments with the use of ultraviolet radiation as a therapeutic measure in the healing of fractures they observed no notable influence. They were unable to demonstrate any constant deficiency in calcium in cases of fracture with nonunion.

#### METHODS

Dogs and rats were selected as the experimental animals. In the case of the dogs, a total of twenty-five, the following plan was adopted:

In group A the fibula on one side was fractured, and then, after it had completely healed, the fibula on the other side was broken in as similar a manner as possible. During the healing of the second fracture, the animal was irradiated.

In group B the procedure was reversed; that is, the animal was irradiated while the first fractured fibula was healing and not irradiated after the second fracture was made.

In group C in seven experiments the two fractures were made not in one animal but in two. This was done not by choice but because of the death of an

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32. Swart, H. A.: The Effect of Irradiated Ergosterol on the Healing of Experimentally Produced Fractures in Animals, *J. Bone & Joint Surg.* **12**:360, 1930.

animal or because the second lesion did not duplicate the first. In these seven experiments in which results from different dogs are compared the animals were similar in form and weight.

In group D in two experiments carbon arc radiation was administered in the same amounts per unit of time during the healing of the two fractures. One of these belongs in group C.

In group E in two experiments no irradiation was given during either healing period. One of these belongs in group C.

In the case of the rat, because large numbers could be readily experimented on and followed simultaneously, a group of from seven to ten animals served as controls for two irradiated groups of a series. The fractures in all the animals were identical. Each animal had only one fracture and one period of healing. Carbon arc radiation, varying in type and amount or in both, was administered to two experimental groups of each series. Determinations were made of the percentage of animals in each group in which the fracture was completely healed at various intervals after the fracture.

*Selection and Care of Animals.*—All twenty-five dogs were healthy young adults of white or light color, with short hair, and varied in size from small to medium. A preexperimental period was allowed for them to become accustomed to their surroundings and to determine the normal levels for calcium and inorganic phosphorus. Their diet consisted of meat scraps and bones obtained daily from the market. They were housed in outside, semiclosed pens, with sufficient space to move around in easily and thus to exercise mildly.

The rats were all healthy albino males from our own colony, between 3 and 5 months of age and weighing between 200 and 300 Gm. at the beginning of the experimentation. They were kept in groups of from seven to ten in large cages, and food (Bal-Ra <sup>32a</sup>) and tap water were allowed ad libitum. Both dogs and rats were frequently weighed.

*Determinations of the Calcium and Inorganic Phosphorus Content of the Serum.*—Blood was aspirated from the femoral veins of the dogs at varying intervals and analyzed for calcium by the method of Clark and Collip <sup>33</sup> and for inorganic phosphorus by the method of Fiske and Subbarow. <sup>34</sup> The calcium and the inorganic phosphorus content were not determined for the rats.

*Experimental Fracturing.*—The fibula was fractured in dogs and rats, an aseptic open osteotomy technic similar to that of Lindsay and Howes <sup>35</sup> and Bors <sup>28</sup> being used. The fibula was chosen because it did not necessitate splinting to keep the ends in alinement, since the tibia acts as a support.

The rats were narcotized with ether in a covered jar and carried lightly during the operative procedure. The leg was prepared for operation by clipping and shaving the hair from the lateral surface and applying tincture of iodine. With the sterile portion of the leg protected by a drape, a longitudinal incision was made and carried down to the fascia at the anterior border of the gastrocnemius. When

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32a. Bal-Ra (obtained from the Valentine Company, of Richmond, Va.) contains: moisture, 9.57 per cent; protein, 29.38 per cent; fat, 5.7 per cent; ash, 9.03 per cent, and carbohydrate, 46.32 per cent.

33. Clark, E. P., and Collip, J. B.: Tisdall Method for Determination of Blood Serum Calcium with a Suggested Modification, *J. Biol. Chem.* **63**:461, 1925.

34. Fiske, C. H., and Subbarow, Y.: Colorimetric Determination of Phosphorus, *J. Biol. Chem.* **66**:375, 1925.

35. Lindsay, N. K., and Howes, E. L.: The Breaking Strength of Healing Fractures, *J. Bone & Joint Surg.* **13**:491, 1931.

the fascia was divided and the soleus retracted, the fibula was exposed to view. The point of a slender probe was placed under the fibula and a cut made on each side with the points of small sharp scissors. In this way a small piece, just short of 1 mm. in length, was removed. In two preliminary series the fibula was fractured by simply transecting it. This, however, proved unsatisfactory as all the fractures healed too rapidly to allow differences in time required for healing to be recognized. The results for these preliminary series are not included in this report.

No ligatures were used, as the procedure was practically bloodless. The fascia and skin were closed with continuous silk sutures. In all cases the animals walked on the fractured leg as soon as they had recovered from the anesthesia.

The procedure for the dogs was similar, being carried out under ether anesthesia given by cone throughout the operation. The muscles and fascia were closed with continuous silk sutures, while the skin was closed with intermittent linen sutures. Although there was usually profuse bleeding from subcutaneous vessels, this was easily controlled by hemostats. The lesions in the dogs were by no means identical, but for each experiment reported they were alike. The type of lesion varied in the different experiments from a deep V to a shallow crescent shape. A pointed bone forceps was used to make the V-shaped lesions and a round-nosed forceps to make the crescent.

The ease with which duplicate lesions of the bone could be made in the rats was in sharp contrast to the condition in the dogs. In the rats the operation described became such a routine that the entire procedure could be carried out with accuracy on an animal in five minutes. In the dogs this situation did not exist. Indeed, even after careful study of the roentgenograms taken immediately after the primary lesion and with the plate before us during the second operation, it proved impossible to make identical or even approximately similar lesions in many cases. This, plus the fact that in several of the well duplicated lesions there was erosion or breaking through of the remaining bone of the shaft, which completely removed all semblance of identity, made it necessary to discard the data for sixteen dogs.

*Irradiation.*—The source of radiant energy was a carbon arc lamp. Sunshine carbons and therapeutic C carbons of the National Carbon Company were used in different series and cases. The lamp was operated at between 24 and 27 amperes, with a potential drop across the arc of from 50 to 60 volts. Detailed information concerning the determination by radiometry of the intensity of such radiant energy and its spectral distribution has been given by Laurens.<sup>9b</sup> Owing to changes in the reflecting surfaces of the lamp, the total energy emitted by the Sunshine carbons varied between 0.59 gram calorie per square centimeter per minute at 1 meter distance, with a distribution of 4 per cent of ultraviolet, 42 per cent of luminous and 54 per cent of infra-red rays, and 0.417 gram calories, with a distribution of 3.1 per cent of ultraviolet, 27 per cent of luminous and 69.9 per cent of infra-red rays. For the C carbons the energy varied between 0.461 gram calorie with a distribution of 5.5 per cent of ultraviolet, 12.6 per cent of luminous and 81.9 per cent of infra-red rays and 0.441 gram calorie with a distribution of 4 per cent ultraviolet, 9 per cent of luminous and 87 per cent of infra-red rays.

During the periods of irradiation the dogs were tied on their backs on rounded dog boards, with their abdomens directly exposed to the rays from the flaming arc, and blindfolded to protect the eyes. The rats were placed in hardware cloth tubes in which they were free to move about but were unable to vary their distance from the flaming arc. The amount of energy received per square centimeter of irradiated surface was controlled and varied by changes in the distance from the arc as well as by the duration of the exposure.

*Roentgenograms.*—Roentgenograms served as the criterion of the healing process. The first picture was taken immediately after the operation, to serve as a record and for study before an attempt was made to duplicate the lesion in another fibula or for comparison to determine how accurate a duplication had been made. Successive roentgenograms were made during the healing process at intervals, greater in the early stages than in the later. When the plate revealed a continuous light shadow, similar to that found in the undamaged shaft and of the same width, the fracture was considered completely healed and fully calcified.

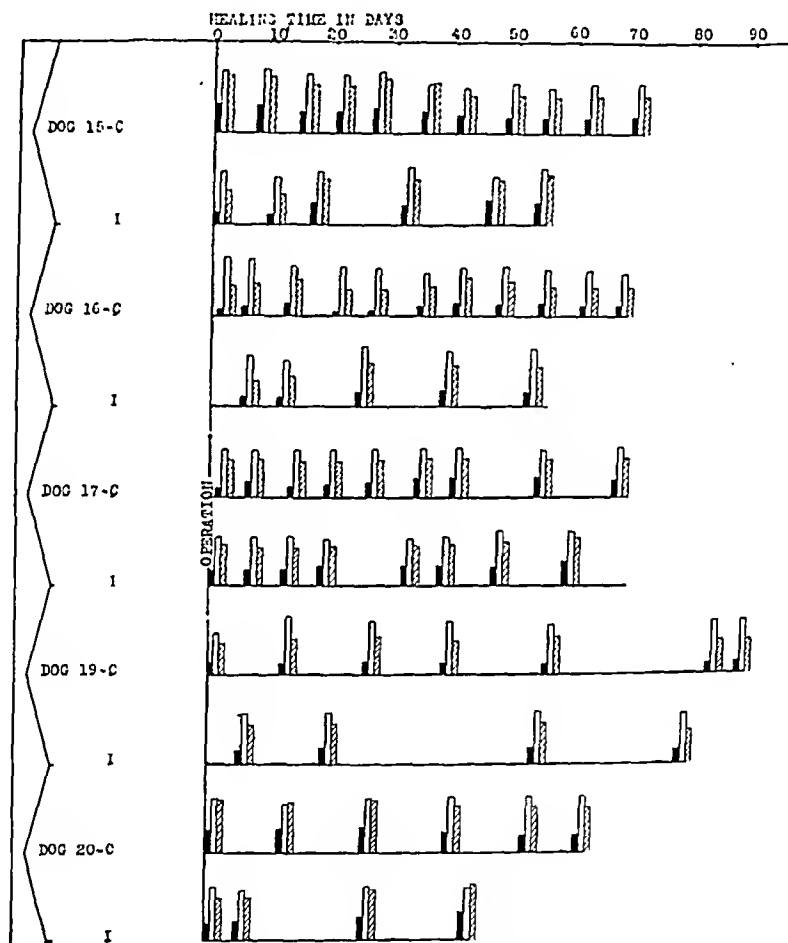


Fig. 1 (group A).—Data on the calcium and phosphorus content of the blood. In figures 1, 3, 4, 6 and 7 the distance between the horizontal black lines represents from 3 to 18 mg. of calcium or of phosphorus per hundred cubic centimeters of blood, or a calcium-phosphorus product of from 0 to 100. The black column indicates the phosphorus content; the white column, the calcium content, and the shaded column, the calcium-phosphorus product. *I* indicates an irradiated animal; *C*, a control animal.

The fact that the callus was not entirely reduced was not considered of significance. Numerous macroscopic examinations of fibulas at autopsy proved that the roentgen criterion was valid.

#### EXPERIMENTAL RESULTS ON DOGS

*Group A.*—In this group each of the five animals (dogs 15, 16, 17, 19 and 20) supplied data for a complete experiment. The control period of healing was

carried out first in all cases, while the experimental period of healing (with irradiation) was second. The type, amount and distribution of radiant energy are incorporated in table 1.

The period of healing by irradiation was shorter than the control period of healing in four animals and equal in the fifth (dog 17). These differences ranged from none to 19 days, with an average of 11.6 days. The serum calcium and

TABLE 1.—Data for the Dogs of Group A

Dog	Irradiation	Diminished Healing Time, Days	Average Increase During Period of Irradiation, Mg. per 100 Cc.			Radiant Energy Received, Gram Calories per Square Centimeter			
			Serum Cal- cium	Inor- ganic Phos- phorus	Calcium Phos- phorus Product	Total	Distribution		
							Ultra- violet	Lumi- nous	Infra- Red
15	Sunshine carbons, 30 min. daily at 100 cm. for 55 days	+16	-0.4	-0.5	-4.9	781.3	31.2	172.2	570.1
16	Sunshine carbons, 30 min. daily at 100 cm. for 56 days	+13	+0.7	+0.1	+8.0	799.6	31.9	191.2	575.5
17	Sunshine carbons, 30 min. daily at 75 cm. for 70 days	+0	+0.5	+0.5	+7.9	1549.9	83.2	555.0	1211.7
19	Sunshine carbons, 30 min. daily at 75 cm. for 81 days	+10	-0.1	+0.6	+10.5	840.5	33.6	326.2	470.7
20	Sunshine carbons, 30 min. daily at 75 cm. for 45 days	+19	-0.3	+0.4	0.0	570.1	23.8	233.3	312.0

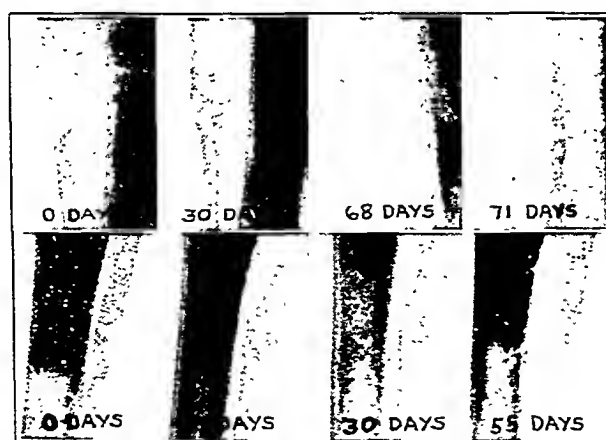


Fig. 2 (group A).—Roentgenograms of the original lesions, two intermediate stages and complete healing of lesions in dog 15. The upper roentgenograms are of the left fibula; the lower ones, the right fibula.

inorganic phosphorus contents remained fairly constant throughout. In three experiments the average serum calcium content was slightly increased during the period of irradiation, while in the other two it was diminished. The average amount of inorganic phosphorus was increased in four and diminished in one of the five experiments. The greatest change that took place in the group in the average content of either calcium or phosphorus was 0.7 mg. per hundred cubic centimeters (table 1). The trends of the calcium, phosphorus and calcium-



phosphorus product were definitely upward during the periods of irradiation in all the experiments, while the opposite trend, or no change, characterized the control determinations (fig. 1).

The total amounts of carbon arc radiation received by each animal during the periods of healing ranged from 1,850 to 570 gram calories per square centimeter, with an average of 968.2 and an average distribution of 4.1 per cent ultraviolet, 31.6 per cent of luminous and 64.3 per cent of infra-red rays. Sunshine carbons were used for all the animals in this series.

The roentgenograms show marked differences in the lesions in the different dogs, but for each dog the two fractures were very similar. In dog 17 the two fractures were almost alike at the beginning, but unfortunately both broke through entirely and in a dissimilar manner. In addition, owing to tension on the leg while the second roentgenogram was being made, the broken ends were drawn farther apart than in the case of the first fracture. The roentgenograms in figure 2 show the original lesions, two intermediate stages and completed healing in the fibulas of dog 15.

TABLE 2.—Data for Dogs of Group B

Dog	Irradiation	Diminished Healing Time, Days	Average Increase During Period of Irradiation, Mg. per 100 Cc.			Radiant Energy Received, Gram Calories per Square Centimeter			
			Serum Cal- cium	Inor- ganic Phos- phorus	Calcium Phos- phorus Product	Total	Distribution		
							Ultra- violet	Lumi- nous	Infra- Red
1	C carbons, 30 min. daily at 75 cm. for 31 days.....	+36	+1.06	+1.2	+16.7	1247.1	46.3	168.8	1032.0
2	C carbons, 30 min. daily at 75 cm. for 31 days.....	+49	0.0	+0.7	+9.2	1247.1	46.3	168.8	1032.0
5	C carbons, 20 min. three times a week at 75 cm. for 49 days.....	—20	+0.8	—0.2	+1.9	381.8	17.9	39.3	324.6
18	Sunshine carbons, 30 min. daily at 75 cm. for 120 days	—20	+0.3	+0.6	+8.6	3028.0	121.1	999.7	1907.2
21	Sunshine carbons, 30 min. daily at 100 cm. for 35 days	+8	+0.7	+1.0	+17.2	525.5	21.0	126.1	378.4

*Group B.*—In this group each of the five animals (dogs 1, 2, 5, 18 and 21) supplied data for a complete experiment. The procedure was the reverse of that used for group A; that is, the period of healing by irradiation was first, and the control period of healing was second. The type, amount and distribution of radiant energy are given in table 2.

The period of healing with irradiation was shorter than the control period of healing in three of the five experiments of this group and longer in two. The difference ranged from 49 days more to 20 days less, with an average of 10.6 days more (table 2). The average changes in the calcium and inorganic phosphorus content of the serum were slight, the greatest being 1.2 mg. The average value for serum calcium increased in four animals during the period of healing by irradiation and was unchanged in the fifth. The average value for inorganic phosphorus increased in four animals and decreased in one (table 2). The calcium-phosphorus product was noticeably higher during the period of irradiation in all cases (fig. 3).

The total amount of radiant energy given to these animals during the first period of healing varied from 3,028 to 381.8 gram calories, with an average of

1,285.9 and an average distribution of 4 per cent of ultraviolet, 19 per cent of luminous and 77 per cent of infra-red rays. Therapeutic C carbons were used for irradiating dogs 1, 2 and 5, and Sunshine carbons for dogs 18 and 21 (table 2 and fig. 3).

The roentgenograms showed that the fractures in the different dogs varied considerably, although they were quite similar in the two fibulas of the individual animals.

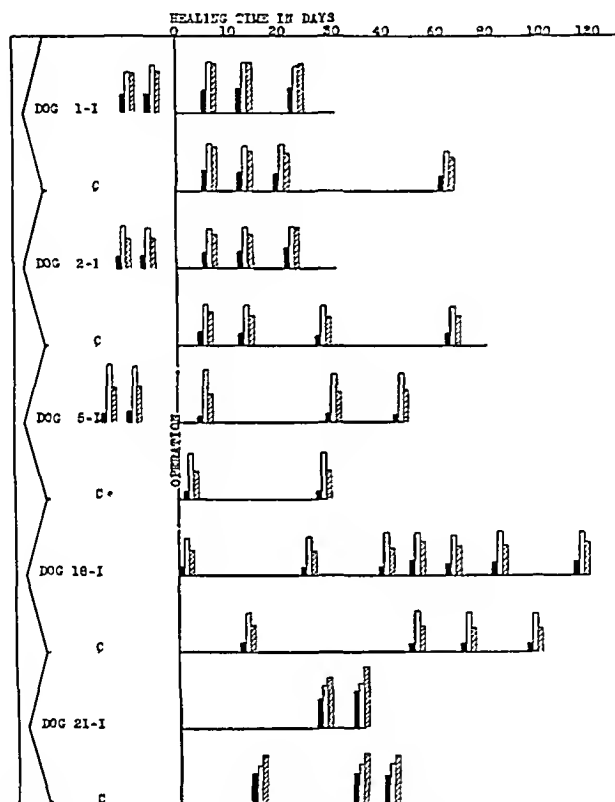


Fig. 3 (group B).—Data on the calcium and phosphorus content of the blood.

*Group C.*—In this group, five pairs (dogs 5 and 4, 13 and 14, 22 and 23, 24 and 25, and 8 and 7) supplied the data. The pairs were selected on the basis of similarity in body build and weight. One of each pair was irradiated during the period of healing of the fracture, while the other was not and served as the control. The type, amount and distribution of radiant energy are given in table 3.

The healing time for the irradiated dog was shorter than that for the control in three of the five pairs of dogs and longer in two pairs. The differences ranged from 19 days more to 24 days less, with an average of 3 days more. The average calcium and inorganic phosphorus contents of the serum of the irradiated animals varied only slightly from that of the controls in the same experiment. The variations were of somewhat greater magnitude than in groups A and B, owing, in part at least, to different basal levels of the animals. (Note the preoperative levels of dogs 13 and 14 [fig. 4].) The trend of the calcium-phosphorus product decreased in only one of the irradiated dogs as compared with its control (pairs

TABLE 3.—Data for the Dogs of Group C

Dog	Irradiation	Dimin- ished Healing Time, Days	Average Increase During Period of Irradiation, Mg. per 100 Cc.			Radiant Energy Received, Gram Calories per Square Centimeter			
			Serum Cal- cium	Inor- ganic Phos- phorus	Calcium Phos- phorus Product	Total	Distribution		
							Ultra- violet	Lumi- nous	Infra- Red
3	C carbons, 20 min. every second day at 75 cm. for 41 days.....	— 5	0.0	—1.3	—13.0	577.0	30.0	68.0	479.0
13	C carbons, 20 min. every second day at 75 cm. for 28 days.....	+19	+0.4	+2.1	+26.0	145.6	7.3	17.5	120.8
22	Sunshine carbons, 30 min. daily at 100 cm. for 35 days	+14	+0.6	+0.2	+2.6	511.2	20.4	117.6	373.2
24	Sunshine carbons, 30 min. daily at 75 cm. for 41 days	+11	—0.7	+1.3	+3.8	1064.0	42.6	297.9	723.5
8	C carbons, 20 min. three times a week at 75 cm. for 11 weeks.....	—24	+0.7	+0.2	+7.3	546.2	23.5	60.1	462.6

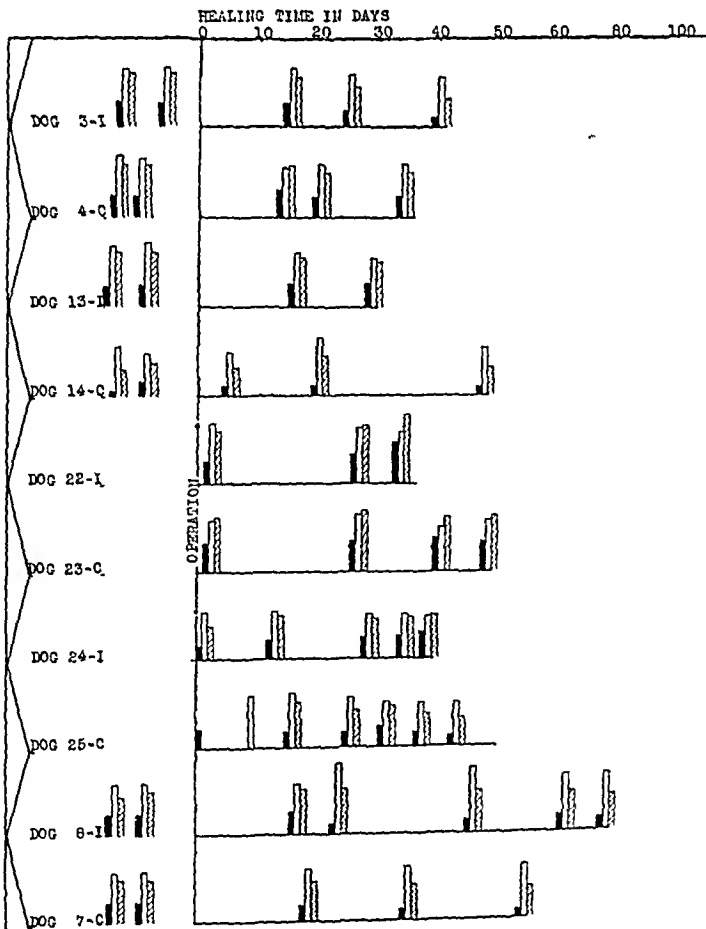


Fig. 4 (group C).—Data on the calcium and phosphorus content of the blood.

3 and 4), and the fracture in the control (dog 4) healed in a slightly shorter time than did that in the irradiated dog (dog 3 [table 3]).

The total amount of radiant energy given to the irradiated animals of this group varied from 1,064 to 145.6 gram calories, with an average of 568.8 and an average distribution of 4.5 per cent of ultraviolet, 17 per cent of luminous and 78.5 per cent of infra-red rays.

*Group D.*—This group consisted of three animals (dogs 6, 8 and 9). In dog 6 both fibulas were fractured, the second after the healing of the first; they were allowed to heal successively, the animal being irradiated in each case. Dogs 8 and 9 had similar lesions and were thus comparable. Both dogs were irradiated during the healing of their fractures.



Fig. 5 (group D).—Roentgenograms of the original lesions of the dogs in this group. The second roentgenogram of dog 9 shows the lesion 167 days after operation.

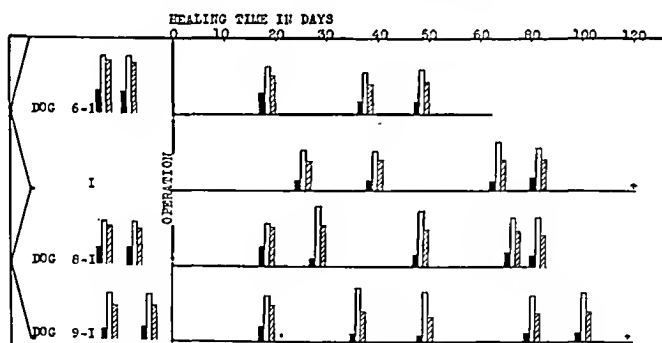


Fig. 6 (group D).—Data on the calcium and phosphorus content of the blood.

The first fracture in dog 6 healed in 64 days, while the second was still not entirely healed in 120 days, thus showing a difference of at least 56 days. The calcium and inorganic phosphorus contents of the serum varied only slightly; enough, however, to make the determinations in the first period of healing show a detectable higher average calcium-phosphorus product (fig. 5).

The healing times were also very different in dogs 8 and 9. The fractures were almost identical (fig. 5), and the body builds of the two animals were very similar. The fracture in dog 8 healed in 81 days; in dog 9 there were still no signs of healing in 167 days after the production of the fracture, thus illustrating true nonunion (fig. 6, table 4).

*Group E.*—The three animals (dogs 12, 10 and 11) in this group were not irradiated. Both fibulas of dog 12 were fractured and allowed to heal successively, as in dog 6, group D. Dogs 10 and 11 had similar lesions and were thus comparable.

TABLE 4.—Data for the Dogs of Group D

Dog	Irradiation	Difference in Healing Time, Days	Average Increase During the Shorter Healing Period, Mg. per 100 Cc.			Radiant Energy Received, Gram Calories per Square Centimeter			
			Serum Calcium	Inor- ganic Phos- phorus	Calcium Phos- phorus Product	Total	Distribution		
							Ultra- violet	Lumi- nous	Infra- Red
6	C carbons, 20 min. three times a week at 75 cm. through both healing periods.....	56+	-0.3	+0.2	+3.1	460.9 543.0	22.1 24.4	49.3 54.3	389.5 464.3
8 and 9	C carbons, 20 min. three times a week at 75 cm. for 11 weeks.....	86+	+0.2	+0.7	+11.3	546.2 546.2	23.5 23.5	60.1 60.1	462.6 462.6

The first fracture in dog 12 healed in 38 days, and the second in 57 days, a difference of 19 days. The serum calcium content was, on an average, 1.1 mg. higher in the longer period of healing, while the inorganic phosphorus was higher by an average of 1.8 mg. in the shorter period of healing. The calcium-phosphorus product was noticeably greater during the shorter period of healing.

In the other experiment of this group there was a difference of 35 days in the healing time. The fibula of dog 10 healed in 35 days, while that of dog 11 took 70 days, or twice as long. The average calcium and inorganic phosphorus contents of the serum were higher in dog 11, and thus the calcium-phosphorus product was also higher in the more slowly healing animal (fig. 7; table 5).

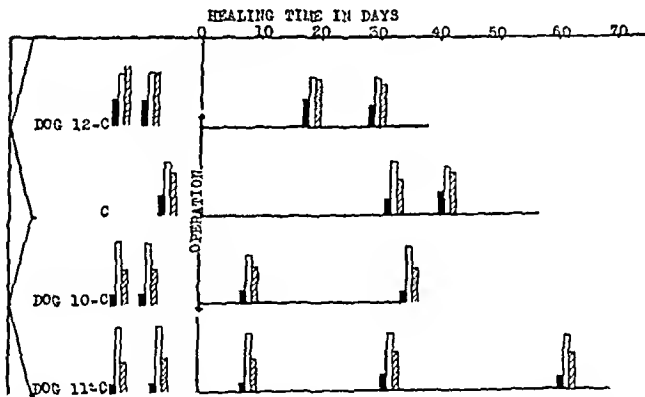


Fig. 7 (group E).—Data on the calcium and phosphorus content of the blood when no irradiation was given during the period of healing.

*Summary.*—In the three groups (A, B and C) there were fifteen pairs of similar fractures. During the healing period of one fracture of each pair, the animal was irradiated. The healing time of the irradiated in contrast to the control fracture was diminished in ten instances, increased in four and equal in one. The average diminished healing time was 8.5 days.

Taking all five groups together, that is, adding groups D and E and contrasting the healing time of the four fractures of the former with

the four unirradiated fractures of the latter, a much different final figure is found. The average difference is a minus figure, or a diminished average healing time of 5.7 days in the controls. The lesions of the bone in group D are in general decidedly more severe than those in group E (figs. 6 and 8). If we omit the two very abnormal periods of healing, namely, the second period for dog 6, group D, and dog 9, group E, still another difference is obtained. The average period for the seventeen remaining periods of healing by irradiation is 55.8 days, while for the nineteen control periods it is 59.5 days; thus there is a difference of 3.7 days in favor of the periods of treatment with irradiation.

TABLE 5.—Data for Dogs of Group E

Dog	Irradiation	Difference in Healing Time, Days	Increase During the Shorter Healing Period		
			Scrum Calcium	Inorganic Phosphorus	Calcium-Phos- phorus Product
12	None.....	19	-1.1	+1.8	+18.0
10 and 11	None.....	35	-0.2	-0.2	- 6.3

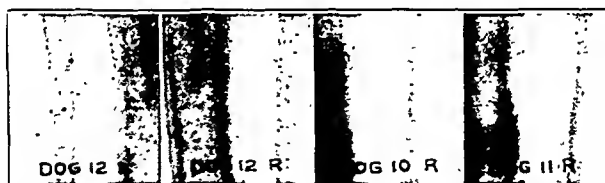


Fig. 8 (group E).—Roentgenograms of the original lesions of the dogs in this group.

The weights, which were taken frequently for all the animals, are not referred to in any of the experiments, for in all cases the curves for weight were well within the range of normal; no correlation was found between the weights and the time of healing.

#### EXPERIMENTAL RESULTS ON RATS

The experimentation on rats was performed in three series; a total of eighty healthy male rats between the ages of 3 and 5 months and weighing between 200 and 300 Gm. at the beginning of experimentation were used. The animals were weighed frequently, and all showed a normal gain; thus the weights are not reported.

In each of the three series there were three groups of from seven to ten animals each. Group 1 of each series was irradiated with Sunshine carbons, and group 2 with therapeutic C carbons; group 3 served as a control.

The lesions of the bone in all the animals were identical. Pictures of the lesions made in the ten animals of group 1 of series 1 show how similarly the lesions of the bone were made.

In all the groups the experiment was terminated about 70 days after operation was performed. The last roentgenogram taken and one taken about the middle of the experimental period are referred to in the results.

*Series I.*—There were thirty animals in this series—ten animals in each group. In group 1, however, two animals were accidentally killed a few days after they were operated on; thus only eight are considered in the experiment.

Group 1 received a total of 571.2 gram calories per square centimeter of Sunshine carbon radiation, with an average distribution of 3.2 per cent of ultraviolet,

TABLE 6.—*Experimental Results with Rats*

Series	Group	Irradiation	Days	Fractures Healed, Number	Fractures Unhealed, Number	Fractures Healed, Percentage	Fractures Unhealed, Percentage
I	1	Sunshine carbons, 30 min., three times a week at 75 cm.	30	5	3	62.5	37.5
			60	6	2	75.0	25.0
	2	C carbons, 15 min., three times a week at 75 cm.	30	2	8	20.0	80.0
			60	3	7	30.0	70.0
	3	Controls.....	30	2	8	20.0	80.0
			60	4	6	40.0	60.0
II	1	Sunshine carbons, 20 min. every second day at 75 cm.	31	6	2	75.0	25.0
			67	7	1	87.5	12.5
	2	C carbons, 10 min. every second day at 75 cm.	31	3	4	42.8	57.2
			67	4	3	57.2	42.8
	3	Controls.....	31	2	8	20.0	80.0
			67	5	5	50.0	50.0
III	1	Sunshine carbons, 20 min. every second day at 75 cm.	45	3	4	42.8	57.2
			73	4	3	67.2	42.8
	2	C carbons, 10 min. every second day at 75 cm.	45	0	9	00.0	100.0
			73	0	9	00.0	100.0
	3	Controls.....	45	2	7	22.2	77.8
			73	3	6	33.3	66.7
Totals	Groups 1 (23 animals).....			17	6	73.9	26.1
	Groups 2 (26 animals).....			7	19	26.9	73.1
	Groups 3 (29 animals).....			12	17	41.3	58.7

28.8 per cent of luminous and 68 per cent of infra-red rays, in the 61 days of healing. Group 2 in the same period of time received 308.5 gram calories of therapeutic C carbon radiation with an average distribution of 5.5 per cent of ultraviolet, 11.0 per cent of luminous and 83.5 per cent of infra-red rays (table 6).

After 30 days of healing, the roentgenograms showed that five, or 62.5 per cent, of the fractures in group 1 were healed; two, or 20 per cent, in group 2, and two, or 20 per cent, in the control group. After 60 days of healing, six, or 75 per cent, of the fractures in group 1 were healed; three, or 30 per cent, in group 2, and four, or 40 per cent, in group 3 (figs. 9, 10 and 11; table 6).

*Series II.*—In this series there were twenty-five animals—eight in group 1, seven in group 2 and ten in group 3.

Group 1 received a total of 510 gram calories of Sunshine carbon radiation with an average distribution of 3.9 per cent of ultraviolet, 33.8 per cent of luminous and 62.3 per cent of infra-red rays during the 67 days. Group 2 received a total of 268 gram calories of therapeutic C carbon radiation with an average distribution of 5.5 per cent of ultraviolet, 12.5 per cent of luminous and 82 per cent of infra-red rays during the period of healing.

At the end of 31 days of healing, the roentgenograms showed that six, or 75 per cent, of the fractures in group 1 were healed; three, or 42.8 per cent, in

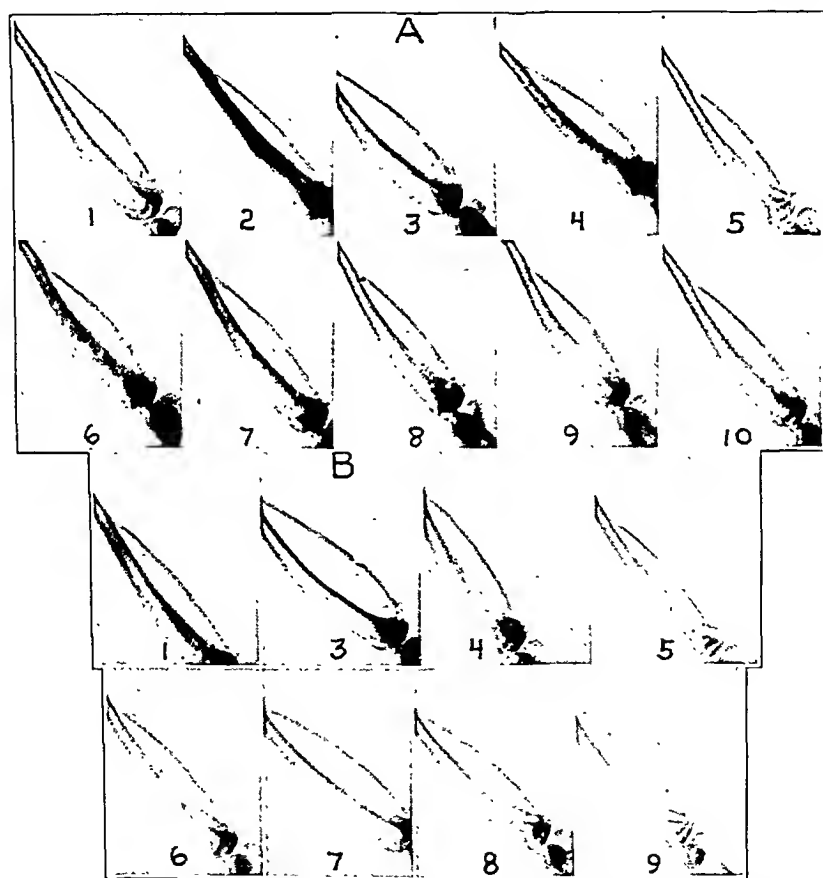


Fig. 9 (series I, group 1).—*A*, roentgenograms of the original lesions of the rats in this group, and *B*, roentgenograms of the lesions 60 days after operation.

group 2, and two, or 20 per cent, in group 3. At the termination of the series, after 67 days of healing, seven, or 87.5 per cent, of the fractures in group 1 were healed; four, or 57.2 per cent, in group 2, and five, or 50 per cent, in group 3 (table 6).

*Series III.*—This series was composed of twenty-five animals; seven in group 1, nine in group 2 and nine in group 3.

During the period of healing group 1 received a total of 550.4 gram calories of Sunshine carbon radiation with an average distribution of 3.6 per cent of ultra-



violet, 32.2 per cent of luminous and 64.2 per cent of infra-red rays. Group 2 received a total of 289.6 gram calories of therapeutic C carbon radiation with an average distribution of 5 per cent of ultraviolet, 11.5 per cent of luminous and 83.5 per cent of infra-red rays during the 73 days.

Roentgenograms taken on the forty-fifth day of the healing period showed that three, or 42.8 per cent, of the fractures in group 1 were healed; none in group 2,

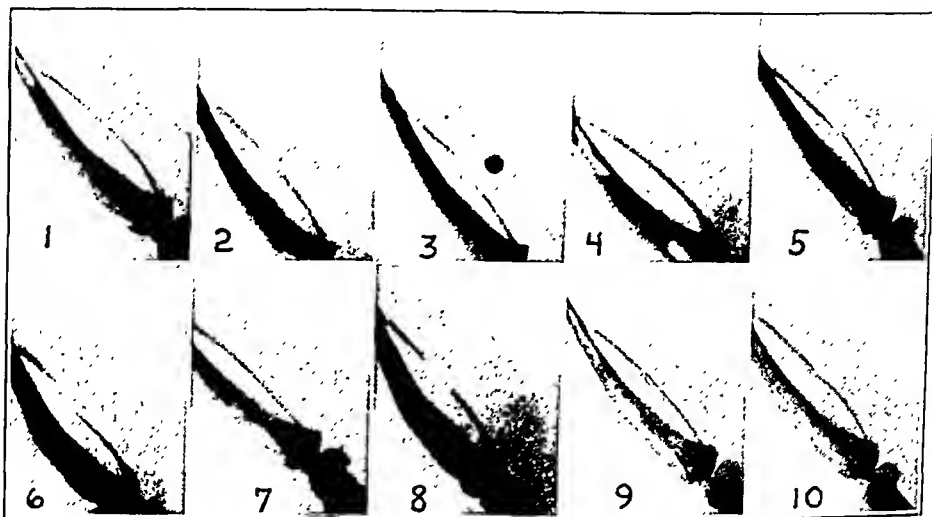


Fig. 10 (series I, group 2).—Roentgenograms of the fibulas of rats 60 days after operation.

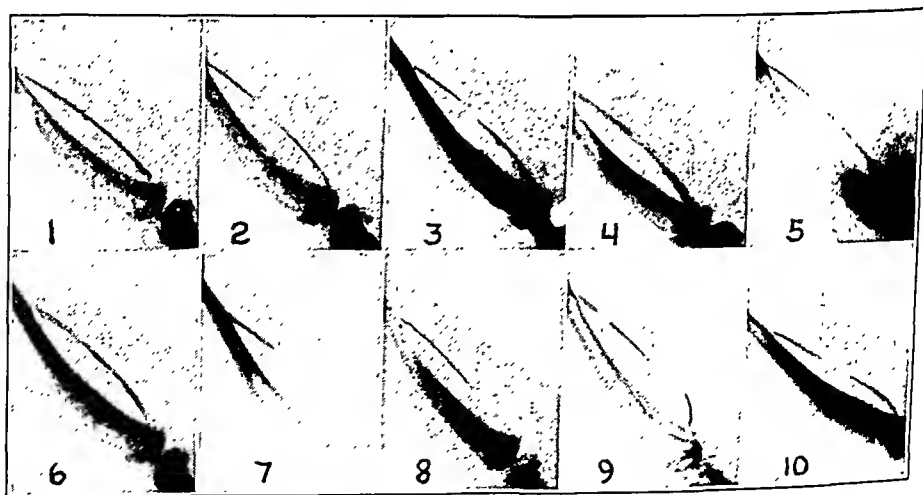


Fig. 11 (series I, group 3).—Roentgenograms of the fibulas of the rats 60 days after operation.

and two, or 22.2 per cent, in group 3. On the 73d day of healing, after which the series was terminated, four, or 57.2 per cent, of the fractures in group 1 were healed; none in group 2, and three, or 33.3 per cent, in group 3.

*Summary.*—Considering all the groups of the same kind together, irrespective of series, a more representative percentage figure is obtained.

This can well be done, for the only factor of difference is a small difference in the sum total of the same type of radiant energy received.

In group 1, composed of twenty-three animals that received Sunshine carbon radiation, seventeen, or 73.9 per cent, of the fractures healed at the time of terminating the respective series; in group 2, composed of twenty-six animals that received C carbon radiation, seven, or 26.9 per cent, of the fractures healed, and group 3, composed of twenty-nine nonirradiated animals, twelve, or 41.3 per cent of the fractures healed in the same length of time (table 6). It is thus evident that in rats Sunshine carbon irradiation hastened healing and that therapeutic C carbon irradiation had no effect or retarded the process of healing.

#### COMMENT

The procedures in groups A and B of the dogs were reversed to test whether the length of time of experimentation was correlated with the rapidity of the healing process. It might be expected that the longer an animal is kept under experimental conditions, the less active is the ability of the bone to regenerate. That this is not true is borne out by considering the results obtained with the dogs in which the fracture went through two processes of healing, namely, groups A and B, dog 6 of group D and dog 12 of group E. Four fibulas in group A (dogs 15, 16, 19 and 20) and two in group B (dogs 5 and 18), a total of six, or 50 per cent, of the twelve considered, healed more rapidly following the second fracture. One fibula, or 8.35 per cent (dog 17), healed in the same length of time, and five, or 41.65 per cent (dogs 1, 2 and 21 of group B, dog 6 of group D and dog 12 of group E), took longer to heal following the second fracture. The nutritional state, as judged from weights and general appearance, was normal for all these animals during the experimentation.

The material of group C, in which two dogs were paired in each experiment, was not planned for, but as it accumulated it was analyzed in order to utilize data on animals in which the two fractures in the same animal did not approach similarity but in which one was much like a fracture in another animal of approximately the same weight and type. Later in the work, however, animals were paired in this way intentionally. It is evident that this group was not so well controlled as were groups A and B, in which each animal served as its own earlier or later control. This, however, is the type of data that must be considered clinically, and thus, from that point of view, may be more valuable than that from the more accurately controlled groups.

Groups D and E were designed to show the amount of variation in healing time which could be expected when the experimental conditions were absolutely similar, namely, when the animals in group D

were irradiated and when those in group E were not irradiated. Unfortunately, the groups were not sufficiently large to justify any far reaching conclusions.

There is no apparent correlation between the calcium-phosphorus product and the rate of healing of a fracture and ossification. This finding, therefore, substantiates the conclusions of Ravdin and Morrison<sup>24</sup> and Speed<sup>25</sup> from work on dogs, namely, that the calcium-phosphorus product cannot be relied on as a prognostic index of the rate of regeneration of bone. In group A, in which the period of healing by irradiation was shorter than the control period in four experiments and the same in the fifth (dog 15, one of the outstanding examples of diminished healing time with irradiation), there was a lower average content of calcium and of inorganic phosphorus in serum, and thus there was a lower calcium-phosphorus product, during the shorter period of healing by irradiation. Dog 19, of the same group, showed equal average calcium-phosphorus products for the two periods of healing, and yet the period of healing was 10 days less for the irradiated fracture (table 1). In group B all the animals showed higher average calcium-phosphorus products during the periods of healing by irradiation, although in two animals (dogs 5 and 18) the fracture healed more rapidly during the control period (table 2).

In the one true instance of nonhealing (dog 9), the amount of calcium and of phosphorus and the calcium-phosphorus product were always well within the range of normal. Indeed, in only one set of determinations did the calcium-phosphorus product fall below 50. This is contrary to the results obtained by Johnson<sup>19</sup> and Petersen,<sup>21</sup> who found that nonunion occurred only in cases in which the calcium-phosphorus product was below 35. On the other hand, it is in accord with the point of view more generally held, namely, that there is no correlation between the calcium-phosphorus product and the rate of healing of the fracture.

We may be criticized for dogmatic statements concerning the exact healing time because the roentgenograms taken near the end of a period of healing were sometimes 10 days apart, so that the exact day on which healing was complete cannot be given more closely than that. However, essentially the same procedure was followed in determining the date of healing of both fractures of an experiment, and thus no unfair advantage can be claimed for either the irradiated or the non-irradiated (control) fracture.

It is questionable whether the accelerated healing produced by irradiation, observed when the irradiated fibulas are contrasted with the controls (8.5 days in groups A, B and C and 3.7 days when groups D and E, less the second period of healing for dog 6 and the period of healing for dog 9, are added), is of either scientific or practical sig-

nificance. However, as Murray<sup>36</sup> said: "The treatment of fractures is today an economic problem. End results are to be estimated in dollars and cents." Thus, the time taken to secure the end-results is of considerable importance, and, as Murray suggested, a diminished period of healing of the order of magnitude here observed may be of practical significance at least.

It must be remembered that the work was done on presumably normal animals with normal bone-regenerating ability. If the work had been carried out on abnormal animals, all other factors remaining constant, the results might have been a great deal different.

The markedly different results obtained in the work with rats with the Sunshine carbon radiation as contrasted with the therapeutic C carbon radiation is of some interest. In every series the total amount of Sunshine carbon irradiation given to group 1 was greater than the amount of therapeutic C carbon radiation given to group 2. When the results in each case were compared with those obtained in the controls, the Sunshine carbon irradiation appeared to aid the process of healing, while the therapeutic C carbon irradiation seemed to retard it. The C carbons emit a higher percentage of ultraviolet and infra-red rays than do the Sunshine carbons, but in no series did the total amount of these portions of the spectrum excel, or even equal, the amounts given when the animals were irradiated with the Sunshine carbons. Thus it seems evident that there was something about the spectrum emitted by the C carbons, and not the total amounts of the different components received by the animals, that was detrimental. Coblenz, Stair and Hogue<sup>37</sup> have shown that C carbons emit a larger percentage of the short ultraviolet wavelengths, which produce more erythema than do the rays from the Sunshine carbons. This greater concentration of the short erythema-producing ultraviolet wavelengths may lead to a more marked vasodilatation with possibly an increase in the volume flow of blood, as has been demonstrated in some cases in dogs.<sup>38</sup> Jones and Roberts<sup>39</sup> expressed the belief that an increased flow of blood is a detriment to healing of the bone, and McMaster and Roome<sup>40</sup> demon-

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36. Murray, C. R.: *Proper Place of Physical Therapy in the Treatment of Fractures*, J. A. M. A. **97**:235 (July 25) 1931.

37. Coblenz, W. W.; Stair, R., and Hogue, J. M.: *Tests of a Balanced Thermocouple and Filter Radiometer as a Standard Ultraviolet Dosage Intensity Meter*, Bur. Stand. J. Research **8**:759, 1932.

38. Pollock, B. E.: *The Effect of Carbon Arc Radiation on the Cardiac Output in Dogs*, Thesis, Tulane University Graduate School, 1933.

39. Jones, R. W., and Roberts, R. E.: *Decalcification and Ossification*, Brit. J. Surg. **21**:461, 1934.

40. McMaster, P. E., and Roome, M. W.: *Effect of Sympathectomy on Bone Repair*, Proc. Soc. Exper. Biol. & Med. **30**:123, 1932.

strated on dogs that lumbar sympathectomy, which brings about vasodilatation of the extremity, leads to retardation in the healing of a fracture.

A discussion of the rôle played by the periosteum and endosteum in the healing of fractures is not believed to be pertinent in this presentation, for in all of the fractures contrasted, the lesions of the bone, and thus the periosteum and endosteum, were similar.

#### SUMMARY

Experimental fractures of the fibula were studied in twenty-five normal dogs and eighty normal rats. All the rats were of similar size and age and sustained like fractures. They were grouped for comparison according to the type and amount of carbon arc radiation received during the period of healing. The fractures in the dogs were paired for comparison only when the two were proved similar or identical by means of roentgenograms: This occurred in the same dog in twelve cases and in two dogs of similar body build and size in seven cases. Measured amounts of carbon arc radiation were given during the period of healing to one fracture of each pair; the other served as a control.

Roentgenograms were taken at intervals to show the progress of healing. For the rats the percentage of fractures healed per group after a certain length of time was ascertained, while for the dogs the total length of the healing process in days was noted. During the periods of healing allowed, 73.9 per cent of the fibulas irradiated with Sunshine carbons, 26.9 per cent of those irradiated with therapeutic C carbons and 41.3 per cent of the controls healed. If two periods of very abnormal healing in the experiments on the dogs are omitted, the average healing time for the fractures was 3.7 days shorter when the animals were irradiated than when they were not.

Determinations of the calcium and the inorganic phosphorus content of the serum were made for the dogs at frequent intervals, but no correlation was demonstrable between them or their product and the length of the periods of healing. The rapidity of the process of healing was not a function of the duration of the experimental conditions of an animal. The weight curves of the animals were all well within the range of normal.

## CLINICAL ASPECTS OF STRUMA LYMPHOMATOSA (HASHIMOTO)

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Struma lymphomatosa (Hashimoto) is a rare type of abnormality of the thyroid gland, first described by Hashimoto in 1912.<sup>1</sup> Because of the infrequency of its occurrence, this type of goiter has been discussed almost exclusively by pathologists who, following Hashimoto's work, occasionally have noted in certain cases the curious histology which he described. By clinicians this lymphoid infiltration of the thyroid is generally considered as a type of chronic thyroiditis, usually Riedel's struma, which it closely resembles in many respects.<sup>2</sup> Since, however, pathologists<sup>3</sup> occasionally report this rare condition, it is of importance that the clinical features of struma lymphomatosa be reviewed and the results of treatment noted.

The fundamental picture in struma lymphomatosa is that of a degenerative change in the thyroid gland, unaccompanied by evidence of acute inflammatory process. Microscopically one sees a diffuse lymphoid infiltration between the follicles, with the frequent formation of secondary nodules. These secondary nodules often reach a large size and ordinarily occupy the central third of a focus of lymphocytic infiltration. There tends to be a variation in the intensity of the lymphocytic infiltration in a gland, ranging from only sparse lymphocytes scattered between colloid-containing follicles, or even absence of infiltration in

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From the Lahey Clinic and the Department of Pathology, New England Deaconess Hospital.

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3. Ewing, J.: *Neoplastic Diseases*, ed. 3, Philadelphia, W. B. Saunders Company, 1928, p. 961. Graham, A., and McCullagh, E. P.: Atrophy and Fibrosis Associated with Lymphoid Tissue in the Thyroid; Struma Lymphomatosa (Hashimoto). *Arch. Surg.* **22**:548 (April) 1931. Smith, L. W., and Clute, H. M.: Chronic Thyroiditis (Riedel's Struma), *Am. J. M. Sc.* **172**:403 (Sept.) 1926. Shaw, A. F. B., and Smith, R. P.: Riedel's Chronic Thyroiditis, *Brit. J. Surg.* **13**:93, 1925. Searls, H. H., and Bartlett, E. I.: Thyroiditis, *California & West. Med.* **24**:639 (May) 1926. Poncet, M. A.: Sur le goître cancéreux et la dégénérescence fibreuse du corps thyroïde, *Bull. et mém. Soc. d. chirurgiens de Paris* **27**:863, 1901.

certain portions of the gland, to complete obscuring or displacement of the normal architecture by confluent masses of lymphocytes, usually presenting a variable number of secondary nodules.

The cells, which sometimes are contained within the colloid of the follicles, normally monocytes, may be lymphocytes in this condition.

The thyroid follicles present tend to be grouped closely together, in many instances so that one sees what might at first appear to be foci of thyroid tissue in a lymph node. However, the organization of the lymphoid tissue into a definite node does not take place; that is, there is no formation of stroma or of sinuses.



Fig. 1 (case 9).—A photograph of the specimens of thyroid gland removed. Note the density of the gland, the preservation of the normal thyroid contour and the numerous fine fibrous septums.

Rarely a few plasma cells appear in the interstitial tissue.

There is ordinarily no involvement of other structures, although occasionally there may be slight enlargement of regional lymph nodes. Splenic enlargement is never encountered.

At times, a marked lymphocytic infiltration simulating this lesion is presented in patients with long-standing hyperthyroidism, particularly in heavily iodized patients, in whom lymphoid infiltration with secondary follicle formation is by no means unknown.

From the diverse range of lymphocytic infiltrations in the thyroid, struma lymphomatosa can best be differentiated by the absence of evi-

dence of marked thyroid hyperplasia and atrophy of the thyroid substance, often accompanied by the peculiarly glossy, acidophilic epithelial cells sometimes seen in degenerative processes.

Fibrosis is rarely a prominent feature in this condition, in contrast to Riedel's struma. A moderate amount is often present, however. While in Riedel's struma fibrosis extends diffusely into surrounding structures, in this disease fibrosis is always limited by the capsule of the gland.

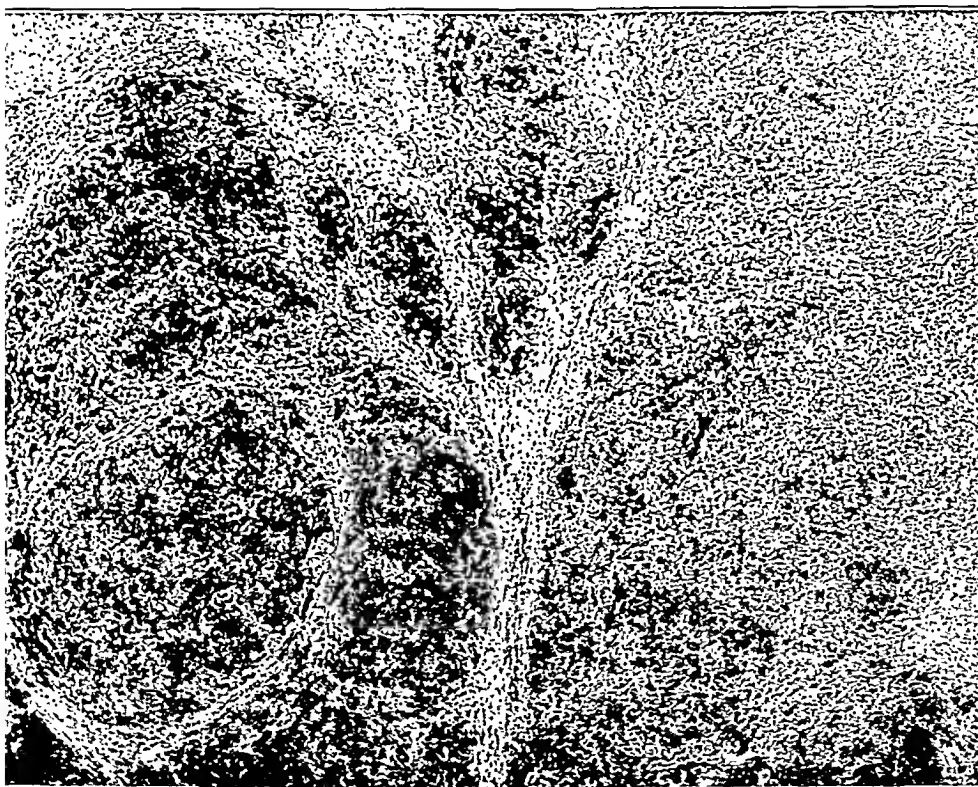


Fig. 2 (case 1).—Photomicrograph ( $\times 50$ ) of a section from the thyroid gland, showing dense lymphoid infiltration and fibrosis and also strands of fibrous tissue. This is an advanced case.

We do not know whether the amount of diffuse fibrosis in the thyroid is related to the duration of the process or not. However, it does seem definitely to be related to the amount of atrophy of the thyroid parenchyma, and as we regard this as secondary to lymphocytic infiltration, the fibrosis is dependent on the degree of lymphocytic infiltration that has taken place.

The suggestion has been made that struma lymphomatosa represents merely one phase in a systemic disease process involving lymphoid



tissue. However, this seems unreasonable in view of the fact that patients suffering from this condition present no generalized disease and the only changes in general constitution are those which can be definitely related to thyroid insufficiency pursuant to the local changes in the glandular tissue or to subtotal thyroidectomy.

Struma lymphomatosa, then, may be regarded pathologically as a lymphocytic infiltration of the thyroid of unknown etiology, inducing an atrophy of the glandular substance and accompanied by a varying degree of interstitial fibrosis. The condition is progressive in the

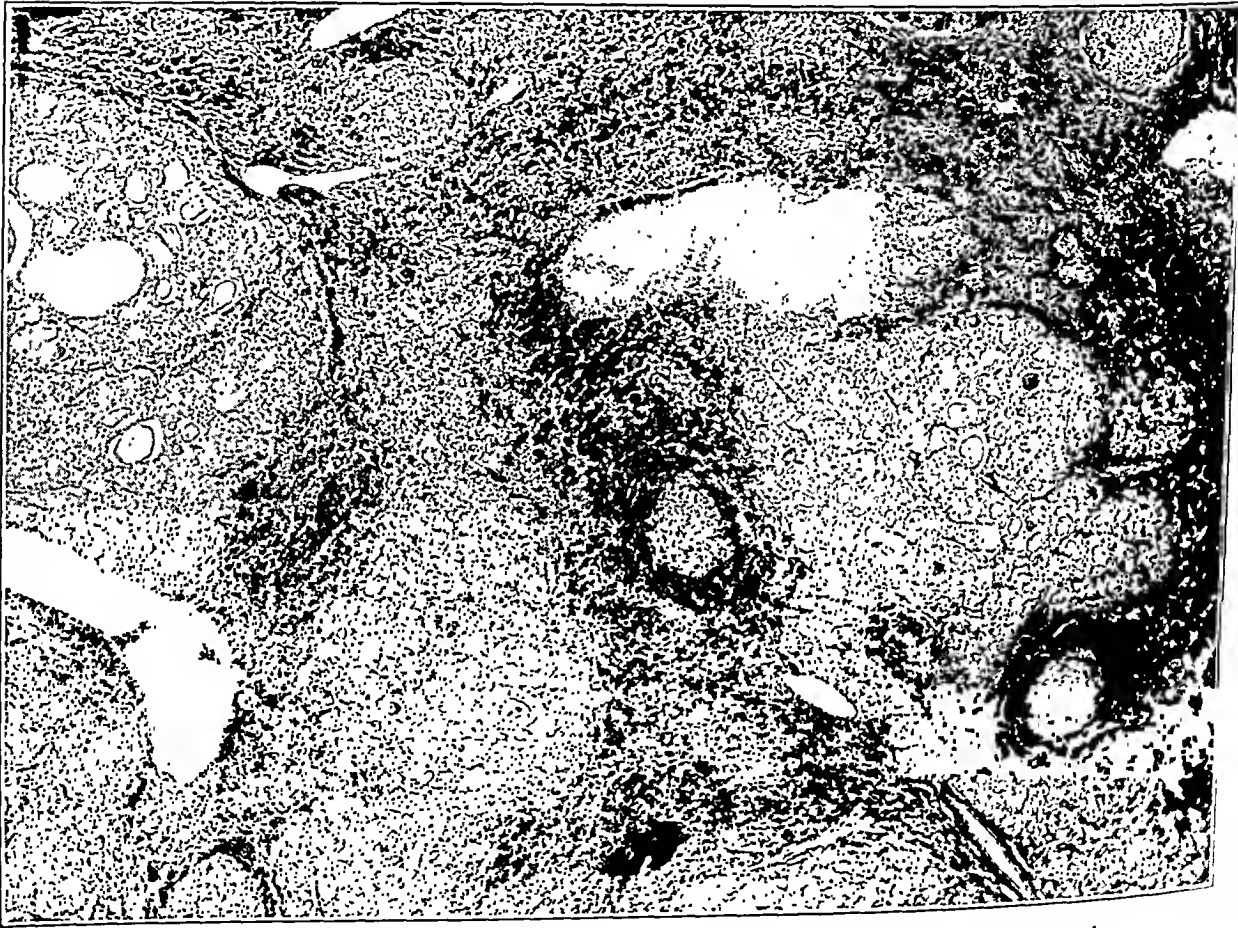


Fig. 3 (case 2).—Photomicrograph ( $\times 50$ ) of a section from the thyroid gland, showing the lymphoid follicles which are practically always present in large numbers with large germinal centers, in which there is active proliferation. In this slide there is also some normal thyroid tissue which is being infiltrated by lymphocytes. This is an early case.

thyroid tissue. Although frequently confused with Riedel's struma, in no instance to our knowledge has it been associated with a malignant process or developed into a malignant process.

We have operated on nine patients with goiter in the past two years who have been found by the pathologist to have struma lymphomatosa.

The clinical symptoms and laboratory findings of these nine patients have been very similar, but it is our feeling that rarely, if ever, are such results so distinctive that a preoperative diagnosis of the true condition can be made.

The nine patients in this series were women. The average age was 55.5 years. The twenty-four patients with Hashimoto's struma whose cases Graham<sup>4</sup> collected from reports in the literature were all women, and the average age was 52.4 years.

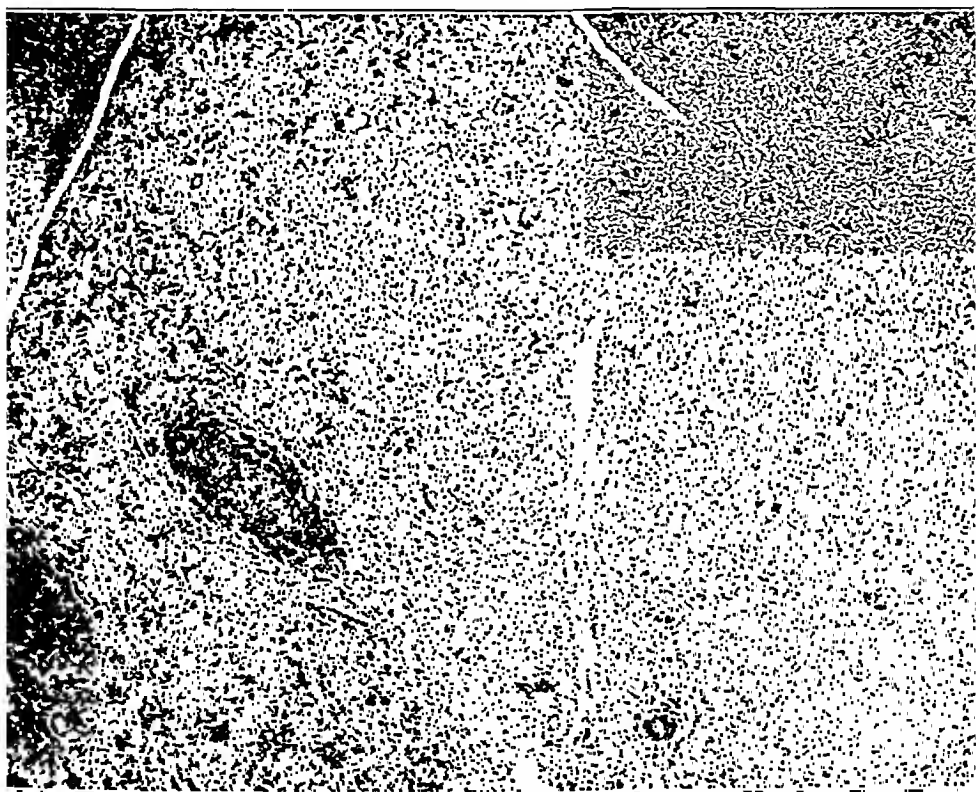


Fig. 4 (case 3).—Photomicrograph ( $\times 50$ ) of a section from the thyroid gland, showing thyroid alveoli but in markedly decreased numbers. There can be little function in the thyroid tissue.

The chief complaint of seven of the nine patients in our group was the presence of the goiter, while pressure on the trachea was the leading symptom of six patients. In general, the gradual appearance of a goiter and the increasing discomfort from the pressure exerted as it grows in size cause most patients to come for treatment. In three of

4. Graham, A.: Riedel's Struma in Contrast to Struma Lymphomatosa, *West. J. Surg.* 39:681 (Sept.) 1931; *Cleveland Clin. Quart.* 1:60 (Jan.) 1932.

our patients some evidence of myxedema was already present at the time of entrance.

On examination a patient with struma lymphomatosa presents a diffusely and symmetrically enlarged thyroid gland from two to six times the normal size. The enlargement generally involves both lobes and the isthmus. Nodules may be palpated, but this is rare. The outstanding finding on clinical examination is the marked firmness or stony hardness of the gland. The resemblance of the condition of the



Fig. 5 (case 5).—Photomicrograph ( $\times 100$ ) of a section from the thyroid gland, showing a typical lymphoid follicle and the lymphoid infiltration among the remaining alveoli. The alveolar epithelium is low and pale, and there is desquamation of it into the alveoli and infiltration by leukocytes.

gland to that in Riedel's struma is so great that it is very doubtful if clinical differentiation is possible. The marked degree of hardness of the thyroid on palpation may suggest a malignant condition in these patients, but the retention of a normal contour of the thyroid and the absence of adherence to surrounding structures are usually sufficiently striking to rule out this diagnosis. No cervical adenitis is present in association with Hashimoto's struma.

The basal metabolic rate of patients with struma lymphomatosa is usually below normal. In three of our nine patients some clinical evidences of myxedema were noted before operation, and the basal rate was below normal in five patients. It is doubtless true that the duration of struma lymphomatosa and degree to which the thyroid acini are replaced by infiltrating lymphoid tissue will determine the amount of thyroid insufficiency noted. In only one patient was the basal rate above normal (+16) and the possibility of thyroid toxicity considered.

It is possible that occasionally a patient with this type of goiter may have mild hyperthyroidism early in the course of the disease. Such a condition is not rare in persons with other types of chronic thyroiditis and is strongly suggested by the symptoms of one of our patients (case 6).

Roentgenograms taken to show the trachea very often reveal a narrowing of this structure by the pressure of the enlarged lateral lobes or of the isthmus. The narrowing of the trachea has never been sufficient to cause stridor, but it has been sufficient to produce a constant sense of discomfort in most patients.

The chief reasons for operating on these patients are, first to relieve the pressure and, second, to make the true diagnosis of the goiter.

At operation fairly characteristic findings are present, and for the first time the surgeon may have suggestive evidence of the true type of goiter which he has encountered. The gland is enlarged from two to five times the normal size and is not adherent to the surrounding structures. In this respect it differs from the gland as it is encountered in chronic thyroiditis and malignant conditions. The gland is firm and grayish pink before it is removed. On section it is white and appears almost edematous in certain areas. Clamps placed in the gland express serous fluid as they are compressed. They hold only to the fibrous capsule of the gland or to the blood vessels in the glandular substance and readily cut through the lymphoid tissue in the body of the goiter.

The operative procedure in the clinic is to treat these patients just as one does patients with chronic thyroiditis of the Riedel type. The pretracheal thyroid tissue is excised widely so that all pressure from the thyroid isthmus on the trachea is relieved. If adequate expansion of the trachea is not obtained by this method, a subtotal thyroidectomy is performed. Large remnants are left on each side, since it is well known that the advancing infiltration of the lymphoid tissue in these cases eradicates the secreting acini of the thyroid and will result in myxedema.

Hashimoto performed subtotal thyroidectomy on his patients and recommended this procedure. In one of our patients (case 3) only the right lobe and isthmus were removed at the first operation, and myxedema developed. In two years, however, the left lobe grew to a large size and caused such symptoms from pressure that it was removed.

# Summary of Clinical Observations on Nine Patients with Struma Lymphomatosa

Name	Sex	Age	Main Symptoms	Presence of Myxedema (Preoperative)	Narrowing of Trachea as Shown by Roentgenograms	Operative Findings	Type of Operation	Post-operative Complications	Presence of Myxedema (Post-operative)	Later Examination
1. B. S.	F	54	Goiter (2 months); dysphagia	Slightly marked pallor; basal metabolic rate, -16	Slight	Thyroid, 4 times normal size; normal contour; no adhesions	Subtotal thyroidectomy	0	Marked myxedema; thyroid extract prescribed	1 year and 10 months later, well except for some numbness of hands; thyroid normal; still on thyroid extract
2. S. L.	F	35	Goiter (1 year); sensation of pressure in neck	No signs; basal metabolic rate, -15	Moderate anterior pressure	Thyroid, 2 to 3 times normal size; very firm; no adhesions	Subtotal thyroidectomy	0	Marked myxedema; thyroid extract prescribed	1½ years later, tired and depressed; cholesterol, 202; still on thyroid extract
3. P. W.	F	47	(first operation) Goiter (3 years); choking spells; nervousness and fatigue	No signs	Narrowed moderately	Right lobe, 2 times normal size; firm and friable; no adhesions	Subtotal thyroidectomy on right side and removal of isthmus	0	Considerable myxedema; thyroid extract prescribed	
		49	(second operation) Goiter on left side (10 months); sensation of pressure	Marked signs; basal metabolic rate, -23; cholesterol, 245	Deviated to the right	Left lobe, 4 times normal size; glistening white; no adhesions	Subtotal thyroidectomy on left side		Marked myxedema; thyroid extract prescribed	8 months later, comfortable; thyroid extract continued; no goiter; voice normal
4. I. G.	F	46	Constriction in neck and windpipe (1 month)	No signs; basal metabolic rate, -19; cholesterol, 168	Deviated to the right	Left lobe, 3 times normal size; right lobe, 1½ times normal size; hard and friable; no adhesions	Subtotal thyroidectomy on left side	0	Considerable myxedema; thyroid extract prescribed	10 months later, well; right lobe, 3 times normal size; left lobe, normal size; no symptoms; thyroid extract stopped

5. H. T.	F	61	Golter (2 months)	No signs; basal metabolic rate, —10	Anterior pressure	Thyroid, 1 to 5 times normal size; nodular; muscles slightly adherent to anterior surface	Subtotal thyroidectomy on right side; partial on left side	0	Started on thyroid extract (postoperative); no myxedema	Röntgen treatment prescribed (postoperative); 6½ months later, well; no myxedema; no thyroid extract taken
6. G. K.	F	51	Nervousness and fatigue (2 months); palpitation; loss of weight	No signs; thought to be slightly thyrotoxic; basal metabolic rate, +10	Anterior pressure	Thyroid, 2 times normal size; unusually firm; no adhesions	Subtotal thyroidectomy	0	Marked myxedema; cholesterol, 510 mg.; thyroid extract pre-scribed	3 months later, general condition good; basal metabolic rate, —2; still on thyroid extract
7. E. W.	F	51	Golter since childhood; large for 2 years; pains in ears	Moderate	?	Thyroid, 2 to 3 times normal size; extremely hard; no adhesions	Partial resection	0	Considerable myxedema; cholesterol, 272 mg.; thyroid extract pre-scribed	1 month later, general condition fair; myxedema present; still on thyroid extract
8. C. P.	F	47	Golter for many years; acute cholecystitis 2 months previously; golter enlarged and harder ever since; stridor (2 months)	No signs; basal metabolic rate, +2	Anterior compression	Thyroid, 4 to 5 times normal size; hard; no adhesions	Resection; removal of isthmus	0	No myxedema	1 month later, general condition good; no myxedema
9. M. H.	F	56	Constriction in neck; dyspnea; hoarseness (1 month); golter in depressed condition 3 years before; improved on thyroid extract	Slight; basal metabolic rate, —13	Lateral and anterior pressure	Thyroid, 3½ times normal size; firm; tense; juicy; no adhesions	Subtotal thyroidectomy	0	Considerable myxedema; basal metabolic rate, —31; cholesterol, 194 mg.; thyroid extract prescribed	Recent case

although myxedema was already present. In another patient (case 4) only the left lobe was removed and examination ten months later showed a marked increase in the size of the remaining lobe, which was very hard and firm. In view of these two cases it may well be that subtotal thyroidectomy is the operation of choice for patients with struma lymphomatosa even though it probably always will be followed by myxedema. The usual care necessary in all operations for goiter must be taken to avoid injuries to the recurrent nerves and to the parathyroids.

The postoperative course is generally smooth and uncomplicated. Brawny thickening of the deep cutaneous layers of the neck, however, persists for from four to six weeks after operation. This has been generally true of patients with all types of thyroiditis on whom we have operated.

In seven of our nine patients myxedema developed after operation, and it was thought to be present for a time in another patient. The one patient in whom myxedema did not develop had only an excision of the thyroid isthmus for the relief of pressure, and her condition has not been followed since operation. It is reasonable to anticipate myxedema following resection of thyroid tissue in these patients, and it is most important that they be forewarned that it may occur. In general it seems to us that these patients are better without the discomfort of the thyroid tumor and with the myxedema controlled by medication than they were before operation. Following the complete operation they are apparently perfectly well as soon as myxedema is controlled. There has been no return of the thyroid tumor in any of our patients after subtotal thyroidectomy.

#### SUMMARY AND CONCLUSIONS

1. Struma lymphomatosa (Hashimoto) is a rare type of chronic thyroiditis marked by a diffuse infiltration of the thyroid with lymphocytes. The pathology is reviewed.

2. The clinical course of the disease in nine patients having this type of goiter is reviewed. It is believed that rarely, if ever, can the diagnosis of struma lymphomatosa be made from clinical examination.

3. The chief disturbance is pressure of the goiter on the trachea. Removal of the isthmus alone may give relief, but continuance of the growth may occur and necessitate further operation. Subtotal thyroidectomy is probably the operation of choice.

4. Myxedema usually follows the subtotal removal of such a goiter and may occur with this disease in the absence of operation.

5. Subtotal thyroidectomy relieves the symptoms caused by pressure, and recurrence of the goiter after this procedure has not occurred.

6. Malignant degeneration in this type of goiter has not been observed among our patients.

## CHRONIC THYROIDITIS

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In 1896 Riedel<sup>1</sup> described a disease of the thyroid gland characterized by subacute, progressive swelling and hardening of the gland and progressive difficulty in respiration. Since that time many cases of benign swelling of the thyroid gland have been reported under the name of Riedel's struma, woody thyroiditis, ligneous thyroiditis or chronic thyroiditis.

In 1912 Hashimoto<sup>2</sup> reported 4 cases in which the subjective symptoms and physical findings were similar to those reported by Riedel but in which the thyroid tissue was replaced by lymphoid tissue. He called this condition struma lymphomatosa. The symptoms of the two conditions are much alike, and cases which are similar to those reported by Hashimoto are frequently reported under the name Riedel's struma.

In 1931 Graham<sup>3</sup> analyzed the cases reported prior to that time. He found reports of 104 cases. Of these, he classified 41 as definite instances of Riedel's struma and 24 as of the Hashimoto variety; he considered 22 as cases of adenoma with fibrosis and inflammation, hyperthyroidism and atrophy and fibrosis, suppuration, tuberculosis and syphilis of the thyroid gland; in the remaining 17 the diagnosis was unverified.

The gross and microscopic pathologic changes, the postoperative course and the complications of operation are different in the two conditions, and it would seem correct to consider them as two different diseases.

In Riedel's thyroiditis there is a progressive, rapid swelling of the gland. Only one lobe is involved in 49 per cent of the cases. The gland may feel smooth or slightly irregular, and it is very hard. Soon there are signs of tracheal pressure; these progress and in the late stages lead to severe attacks of asphyxia, which may be fatal. The regional lymph glands are rarely enlarged. In moderately advanced cases the borders of the thyroid are hard to distinguish accurately because of adhesions. There is no involvement of the skin. In advanced cases, hoarseness, dysphagia, recurrent nerve paralysis and signs of involvement of the great vessels may be seen. Occasionally the gland

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1. Riedel: *Verhandl. d. deutsche Gesellsch. f. Chir.* **25**:101, 1896.

2. Hashimoto, H.: *Arch. f. klin. Chir.* **97**:219, 1912.

3. Graham, A.: *West. J. Surg.* **39**:681, 1931.



is tender. The white blood cell count is usually from 10,000 to 15,000 per cubic millimeter. The Wassermann and tuberculin tests give negative results. The average age is 39 years, and 44 per cent of the cases occur in men.

At operation in cases of Riedel's struma inflammatory adhesions are found between the capsule and the adjacent strap muscles. These may be very hard, and it may be impossible to find any line of cleavage. The tumor grasps the trachea as in a vise. The adhesions are usually very vascular, but within the capsule the tissue is often relatively avascular. There may be involvement of the trachea, carotid artery, internal jugular vein and recurrent laryngeal nerve.

The surfaces made by cutting are yellow-white. Microscopically, the normal glandular structure is almost entirely replaced by connective tissue. There is an extension inward of the capsular connective tissue. In places foreign body giant cells are found surrounding small bits of colloid. The predominant cell is the connective tissue cell, but there is a variable amount of infiltration with lymphocytes and plasma cells. In some fields no normal thyroid tissue can be seen.

The disease described by Hashimoto is almost always found in women, only 1 case having been reported in a man.<sup>4</sup> The average age incidence is 53 years. The chief symptom is rapidly increasing swelling of the thyroid gland. It almost always involves both lobes. There are seldom any adhesions to the adjacent muscles. At operation the gland can be freed without great difficulty. It is hard and smooth or slightly nodular. It is enlarged, retaining the form of the normal thyroid gland. Pressure over the trachea may be moderate, but the gland can be freed without great difficulty. On section the gland is divided into lobules by dense fibrous trabeculae. It cuts with difficulty. Microscopically there are an extensive diffuse infiltration with lymphocytes and numerous localized areas of lymphoid tissue with hyperplastic germinal centers. A few multinucleated foreign body giant cells may be present. There is an increase in connective tissue, but the tissue resembles a lymph gland, and there is very little colloid or normal thyroid tissue.

The following tabulation gives the chief differential points:

	Riedel's Struma	Struma Lymphomatosa
Average age.....	39 years	53 years
Sex .....	44 per cent males	4 per cent males
Average duration of symptoms.....	11 months	14 months
Unilateral involvement.....	49 per cent	Rare
Markedly adherent.....	78 per cent	None
Tracheotomy .....	22.2 per cent	None
Deaths .....	6	None
Postoperative hyperthyroidism.....	19.9 per cent of 32 cases	58 per cent of 19 cases

4. Meeker, L. H.: *Am. J. Path.* 1:57, 1925.

Ewing stated that struma lymphomatosa is an early stage of chronic woody thyroiditis. However, as Graham pointed out, it seems unlikely that struma lymphomatosa is an earlier stage, since it tends to occur in older persons and since it tends to involve both lobes, whereas in the supposedly later stage the involvement is unilateral in 49 per cent of the cases.

Graham expressed the opinion that Riedel's struma is a local inflammation in the thyroid, the general bodily state being affected only secondarily by reason of destruction of thyroid tissue, respiratory difficulty or injuries to important blood vessels and nerves. He described struma lymphomatosa as a local manifestation of a constitutional disorder of unknown etiology. In this condition there are degenerative changes in the thyroid rather than inflammatory changes, and ultimately they are accompanied by more definite inflammatory phenomena of a nonspecific nature. The lymphoid tissue, which is variable in amount and to a less degree in character, is nonspecific for struma lymphomatosa.

The differential diagnosis rests between malignant changes, syphilis and tuberculosis. In cases of carcinoma of the thyroid, if there is involvement of the adjacent structures there is almost always involvement of the skin.<sup>5</sup> Carcinoma tends to start in one lobule and does not involve an entire lobe or gland uniformly. It tends to be much more nodular. It is very sensitive to roentgen treatment, whereas chronic thyroiditis is not. If there is doubt about the condition's being carcinoma of the thyroid, it is likely to be chronic thyroiditis, according to Payr.<sup>6</sup>

Vogel<sup>7</sup> stated that syphilis of the thyroid may show a diffuse sclerosis or gumma. The latter is hard to differentiate from a tumor. Congenital syphilis is always associated with visceral lesions. In tertiary syphilis the thyroid is hard, but it is always smaller and does not present a surgical problem. The Wassermann test and therapeutic tests will help in the diagnosis.

Tuberculosis of the thyroid gland is always secondary, according to Vogel. The disease is either miliary, with multiple gray or grayish-white nodules throughout the gland, or of the caseonodular form with small abscesses. There is almost always evidence of systemic tuberculosis.

#### REPORT OF A CASE

Mrs. S., aged 40, entered the Presbyterian Hospital on Oct. 13, 1932, complaining of exhaustion for seven months, slight enlargement of the thyroid for fifteen years, with increasing enlargement, especially on the right side, for the

5. Smith, L. W., and Clute, H. M.: *Am. J. M. Sc.* **172**:403, 1926.

6. Payr, E. L.: Report of International Conference on Goiter, 1927, Bern, H. Huber, 1929, p. 103.

7. Vogel, W.: *Ergebn. d. Chir. u. Orthop.* **23**:317, 1930

past seven months; numbness and tingling of the hands and feet for six months, with swelling of the hands and feet in the morning for two months; hoarseness for six months; severe headaches over the entire head for several months, and daily fever for four weeks starting six months previously. The blood test for undulant fever was questionably positive on one occasion. The systemic history was normal except for the occurrence of hay fever, which had been markedly relieved by serum treatment three years before.

The physical examination revealed a moderately well nourished woman whose general physical condition was normal except for the fact that the thyroid was markedly enlarged, the right side more than the left. It was irregular in outline, and especially near the midline the consistency of the right lobe was unusually firm. It was not fixed. No large glands were palpable. There was an increased transverse dullness just below the suprasternal notch.

The laboratory findings were: temperature, normal; pulse rate, 44 to 80; respiratory rate, 16 to 20; hemoglobin, 88 per cent; red blood cell count, 4,240,000 per cubic millimeter; white blood cell count, 10,800; differential count, normal; blood pressure, 90 systolic and 66 diastolic; stool and urine, normal; Ewald's test, 45 per cent free acid and 70 per cent total acid; roentgenogram of chest, normal; sinus arrhythmia and myocardial damage on electrocardiograph tracing; metabolic rate, -22 and -24. The diagnosis by Dr. R. C. Brown was "a probable carcinoma of the thyroid."

Operation was performed on Oct. 17, 1932, by Dr. V. C. David. A Kocher incision was made with transverse division of the strap muscles. The right upper pole was freed from the surrounding parts with difficulty, and the artery was ligated. Biopsy of the right lobe with frozen sections showed "probable carcinoma." Therefore, a complete thyroidectomy was carried out. This was difficult owing to the fact that the thyroid very intimately surrounded the trachea but nowhere involved it. Two cigaret drains were left through the strap muscles.

A report of the macroscopic examination was made by Dr. David: "A uniform hard, boardlike thickening of the entire thyroid gland, especially involving the right and left lobes, was present. All regions except the pyramidal lobe were involved in this thickening and stonelike hardness of the gland. The gland appeared white and cut with increased tension. No colloid was visible. There were no metastases to the surrounding areas."

The results of the microscopic examination were reported by Dr. H. A. Oberhelman: "The specimen, weighing 70 Gm., consists of the left and right lobes and the isthmus of the thyroid gland. The left lobe is entirely enclosed by a thin fibrous capsule. It is very hard and is made up of irregular nodules up to 3 mm. in diameter. The cut surface of the right lobe is grayish yellow, except in a region 1.9 cm. in diameter near the upper pole, which is brownish yellow, soft and well demarcated from the surrounding tissue. The remainder of the lobe is hard. In serial sections through the back wall of the gland near the upper pole there are two small bright red regions, one just beneath the capsule and the other within the substance of the gland. The isthmus is uniformly hard and yellow.

"In all microscopic sections there is marked replacement of glandular tissue by connective tissue. In most of the sections no acini are present. There is dense round cell infiltration in all areas with several germinal centers. About 5 per cent of the area contains acini. They vary in size up to 0.2 mm. They can scarcely be distinguished from the surrounding connective tissue. The epithelial cells have very little cytoplasm, and the lumens contain a dark red material.

"The diagnosis is Riedel's struma."

The postoperative course was as follows: maximum temperature, 100; temperature normal on the fourth day; pulse rate, 60 to 74; respiratory rate, 16 to 20. The patient left the hospital on the nineteenth postoperative day. As postoperative medication thyroid extract was given as follows: 2 grains (0.13 Gm.) every four hours for the first six days;  $2\frac{1}{2}$  grains (16 Gm.) twice a day from the seventh to the eleventh day, and  $2\frac{1}{2}$  grains daily from the twelfth to the sixteenth day. On the second postoperative day an almost constant severe head-

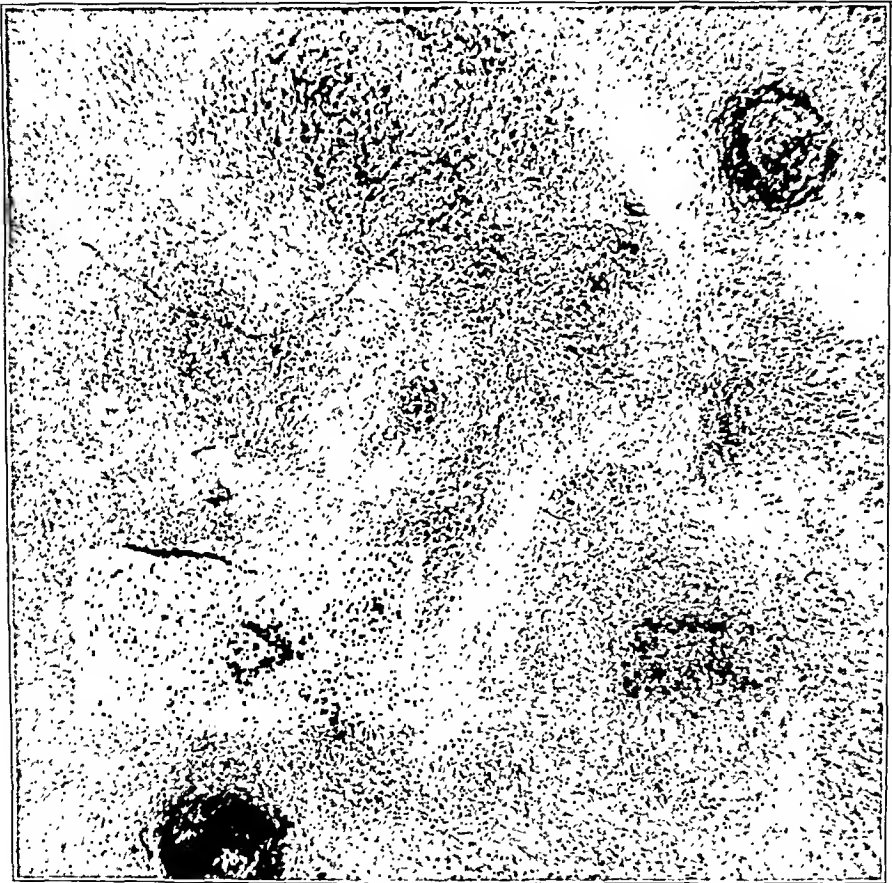


Fig. 1.—Photomicrograph (low power) showing predominance of connective tissue. Three areas of lymphoid hyperplasia are seen.

ache developed over the entire head. There were no signs of tetany. The serum calcium was 7.8 mg. per hundred cubic centimeters. The patient was given 1 cc. of parathyroid extract daily by hypodermic injection and  $\frac{1}{2}$  drachm (1.94 Gm.) of calcium lactate four times a day. On the third and fourth days the serum calcium was 8.5 mg. The headache was still present. The blood pressure was 90 systolic and 54 diastolic. The administration of parathyroid extract was stopped. The headache became more severe, and on the sixth day the serum

calcium was 8.7 mg. Parathyroid extract was again given for two days, with almost complete disappearance of the headache. On the fourteenth day the serum calcium was 9.5 mg., and the patient was receiving 1 cc. of parathyroid extract daily. When the patient was discharged the metabolic rate was  $-13$  and the blood pressure was 98 systolic and 58 diastolic. She was discharged with the following medication prescribed: thyroid extract, 1 grain (0.064 Gm.) twice a day; calcium lactate, 30 grains, three times a day, and a preparation of parathyroid hormone, 1 cc. twice weekly.

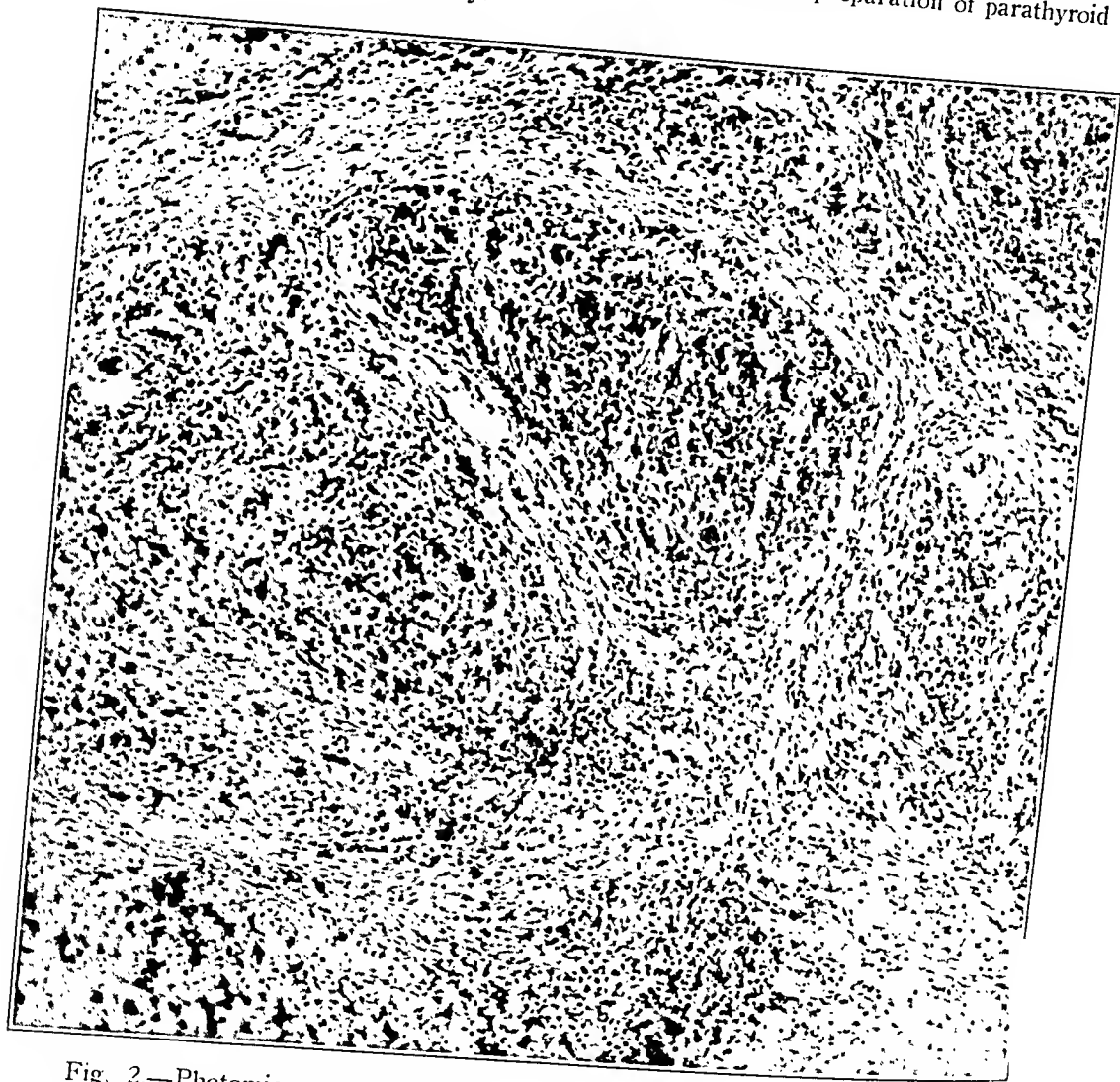


Fig. 2.—Photomicrograph showing extreme atrophy of glandular tissue and replacement by fibrous tissue and infiltration of plasma and round cells.

The patient was seen frequently after she left the hospital, and in January 1933, ten months after the operation, the metabolic rate was normal. She was taking thyroid extract, 1 grain three times a day. The blood calcium varied from 9 to 10 mg. She was taking calcium gluconate, 30 grains (1.9 Gm.) daily. Administration of the preparation of parathyroid hormone had been discontinued six months after she left the hospital. The blood pressure ranged from 90 systolic and 60 diastolic to 100 systolic and 68 diastolic. Headaches were infrequent but

were severe and of a migraine type. The hemoglobin content was 70 per cent; the red blood cell count, 4,400,000, and the white blood cell count, 8,000.

In October 1934, two years after the operation, she returned for treatment of migraine headaches, which were present almost daily. She had less endurance than before her operation but was able to lead a moderately active life. Transient numbness and tingling were present in her arms, hands and feet whenever she reclined. The pulse rate was from 56 to 78; the respiratory rate, from 16 to 20; the red blood cell count, 3,800,000; the hemoglobin content, 68 per cent; the

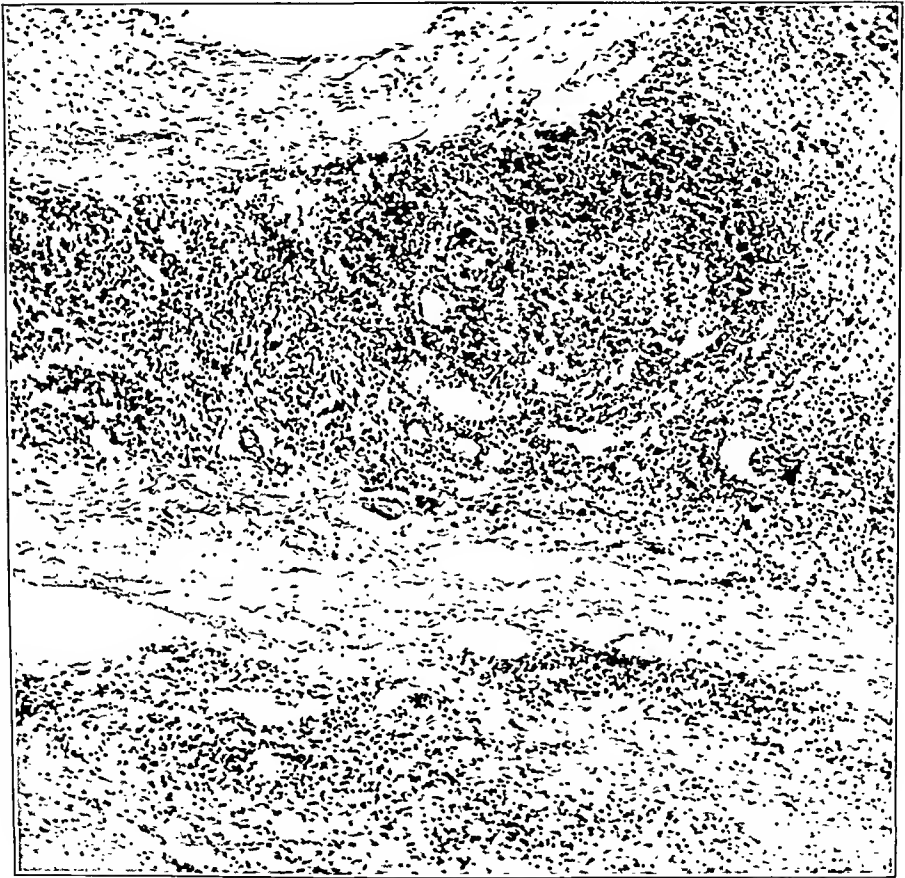


Fig. 3.—Photomicrograph showing one of the few areas containing colloid.

white blood cell count, 8,300; the blood pressure, 104 systolic and 78 diastolic; the weight, 133 pounds (60.3 Kg.); the basal metabolic rate, —19; the serum calcium, 10.2 mg.; the result of the Ewald test, free acid, 35 per cent, and total acid, 55 per cent.

Most authors agree that a thin wedge-shaped resection of each lobe is all that is required, except for freeing the trachea if it is constricted. Recurrence of constriction after removal of tissue for biopsy or incision

is rare. Crile<sup>8</sup> and Payr advised high voltage roentgen therapy after operation, but Payr said that it is useless in cases of struma lymphomatosa. In view of the high incidence of postoperative hypothyroidism, it seems advisable to save a large part of the gland unless the pre-operative basal metabolic rate is high.

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8. Crile, G., and others: *Diagnosis and Treatment of Diseases of the Thyroid Gland*, Philadelphia, W. B. Saunders Company, 1932.

# PHARYNGOGENIC HEMATOGENOUS STREPTOCOCCIC PERITONITIS

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A review of the literature on primary streptococcic peritonitis reveals a maze of conflicting opinions with regard to terminology, pathogenesis, general pathology and therapy. There is a dearth of data of accurately controlled experiments. It is with the expectation of clearing up some disputed points that we submit the following clinical, pathologic, immunologic and experimental study of eight cases of pharyngogenic hematogenous streptococcic peritonitis.

Pharyngogenic hematogenous streptococcic peritonitis is a metastatic inflammatory lesion of the peritoneum caused by a streptococcic hematogenous invasion from a primary focus in the tonsils and pharynx. The disease is characterized by an abrupt onset during or after the subsidence of an infection in the throat, great toxicity, short duration and usually fatal termination.

## CLINICAL AND PATHOLOGIC STUDIES

In the following protocols only the relevant clinical and pathologic data are given.

### REPORT OF CASES

CASE 1.—*History and Course*.—R. H., a married woman aged 33, was admitted to the hospital on March 3, 1934, with a history of pain of forty-eight hours' duration in the lower portion of the abdomen and in the loins, likened by the patient to "labor pains." There was persistent vomiting, but no bowel movement occurred for twenty-four hours. Five days prior to the onset of symptoms the patient had acute tonsillitis with subsequent complete subsidence of symptoms. On admission to the hospital the patient appeared to be acutely ill and distinctly dehydrated. The abdomen was distended and extremely tender, and there was a transverse band of rigidity across the midline. Spasticity of the abdominal wall was a prominent feature. The blood pressure was 70 systolic and 40 diastolic.

Operation by Dr. Auster on March 3 disclosed a large amount of thick, greenish-yellow pus in the abdomen and pelvis. The intestines were markedly hemorrhagic and moderately distended. Fibrinous plastic adhesions were present about the ileocecal region. The uterus and adnexa appeared to be intensely injected. Appendectomy with drainage was performed.

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Dr. A. B. Clements and Dr. W. Wolarsky assisted in the gross postmortem examinations.



The temperature, which on admission was 103.2 F., remained high, with a tendency to a slight increase in the peak each day until 105.6 and 107.6 F. were reached on the fourth and fifth day, respectively. The pulse rate varied between 130 and 160 and was of poor quality. Aspiration of the stomach yielded 1,600 cc. of dark brown fluid with a fecal odor. Death occurred on the fifth day of hospitalization, seven days after the onset of acute abdominal symptoms and two weeks after an attack of tonsillitis.

*Laboratory Data.*—The leukocyte count on March 3 was 15,000, with 85 per cent segmented forms, and on March 6, 8,600, with 88 per cent segmented forms. A blood culture on March 6 gave negative results. On March 3 and 6 albumin, red and white blood cells and hyaline and granular casts were noted in the urine. A culture of pus from the abdomen yielded *Streptococcus alpha* (viridans).

The appendix was 4 cm. in length. The vessels were prominent. Many petechial hemorrhages were present on the serosal surface, which was covered with purulent exudate. Sections showed intense hemorrhagic and purulent periappendicitis with invasion of the muscular coat.

*Postmortem Examination.*—The anatomic diagnosis was diffuse plastic peritonitis, ulcerative jejunitis, colitis and congestion of the lungs, liver and spleen.

The peritoneal cavity was filled with a thick, greenish-yellow plastic exudate and a thinner yellowish fluid. Recent fibrinous adhesions were present between the visceral and parietal peritoneum. Loops of intestine were bound together by exudate. There was no evidence of formation of an abscess. The small intestine was distended, and in the jejunum there were three transversely situated reddened ulcerated areas surrounded by an adherent greenish-yellow membrane. The large intestine was distended and congested. Throughout the colon, but most marked in the descending and sigmoid portions, were many superficial areas of ulceration, each surrounded by an adherent greenish-yellow membrane. The appendicular stump exhibited no noteworthy pathologic change.

*Histopathologic Observations.*—The pulmonary capillaries and arterioles exhibited marked congestion. The liver showed extensive hydropic degeneration of the parenchyma, chiefly at the periphery of the lobules. Massive hyaline thrombosis was present in the splenic pulp. The renal glomerular tufts were congested, and the tubules were intensely hemorrhagic. Marked hemorrhagic oophoritis was present with a periovarian extracapsular purulent exudate.

*CASE 2.—History and Course.*—N. N., a boy aged 4½ years, was admitted to the hospital on May 6, 1934, with a history of sore throat and fever for seven days and otitis for four days. On the second day of illness the temperature was 106 F. For the preceding two days epistaxis was noted.

On admission the child appeared acutely ill. The throat was red, and the cervical lymph nodes were enlarged and tender behind the angle of the jaw on both sides. The right ear drum was red and bulging and there was a slight bloody discharge. A myringotomy was done a few hours after admission. During the night the patient vomited and had several loose bowel movements, following which there developed a typical acute condition in the abdomen. The temperature, which on admission was 103 F., rose to 105.6 F.

On the following day an exploratory operation was performed by Dr. S. Cohn. Over the entire peritoneum, between the intestinal coils, beneath the liver and in the pelvis was a thick creamy purulent exudate. The lymph nodes in the ileocecal region were enlarged to approximately 2 by 1.5 cm. The appendix appeared to be involved by contiguity. Appendectomy with drainage was performed.

The postoperative course was characterized by profound toxemia. The temperature ranged between 103 and 105.2 F., with an average of approximately 104 F.

The pulse rate varied between 120 and 168. Death ensued on the fourth day of hospitalization, four days after the onset of acute abdominal symptoms and eleven days after an attack of sore throat. It may be of interest that multiple watery stools were noted during the entire stay in the hospital, often as many as five during the night. On the day preceding death the body was covered with a toxic rash.

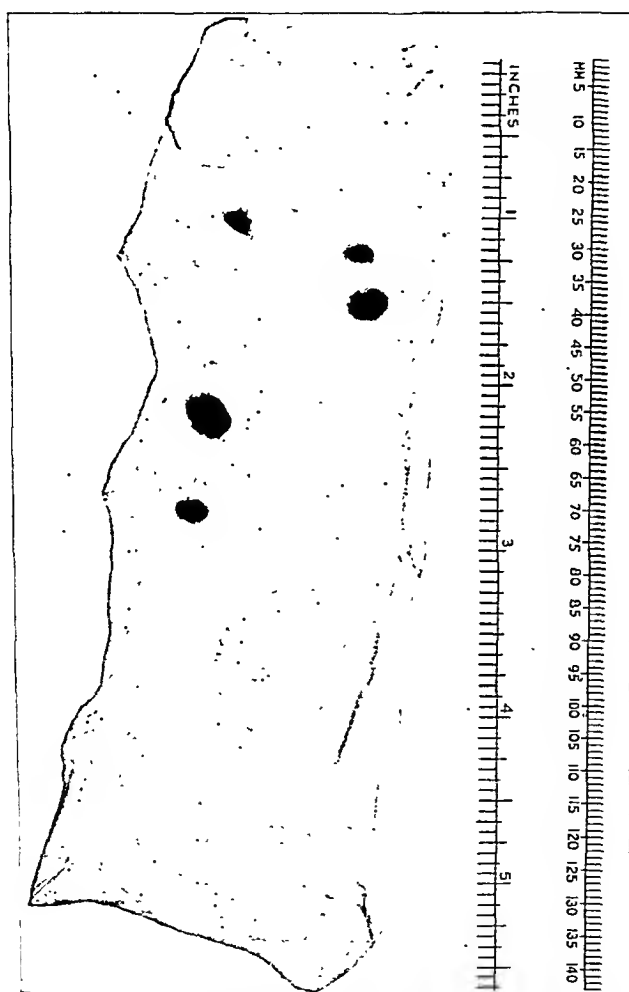


Fig. 1 (case 2).—Intestinal lesions. Note the multiple focal hemorrhagic areas of necrosis and hyperplastic Peyer patches.

*Laboratory Data.*—The leukocyte count on May 6 showed 30,100, with 86 per cent segmented forms. On May 9 albumin, acetone and granular casts were noted in the urine. A culture of the peritoneal fluid yielded Str. alpha (viridans).

The appendix was 6 cm. in length. The serosal vessels were prominent; the coat appeared to be injected. Sections showed periappendicitis with marked con-

gestion. Hemorrhagic infiltration of the mucosa with free blood in the appendicular lumen was noted.

*Postmortem Examination.*—The anatomic diagnosis was diffuse plastic peritonitis, acute perisplenitis, acute hemorrhagic enterocolitis, mesenteric adenitis and bilateral bronchopneumonia.

The abdominal cavity contained straw-colored fluid, and covering the intestines was thick, yellowish, flaky, purulent exudate. In the region of the cecum were many fresh fibrinous adhesions. The mesenteric nodes were enlarged throughout the abdomen. The spleen was covered by a thick, yellowish, purulent membrane. On section the organ was dark red and hemorrhagic and the malpighian corpuscles were prominent. The intestines, beginning with the proximal portion of the



Fig. 2 (case 2).—Photomicrograph of an intestinal lesion. Note the triangular area of hemorrhagic necrosis with the base on circular muscularis. The ulcerated mucosa has been cast off.

jejunum, exhibited a diffusely hemorrhagic mucosa, and Peyer's patches were greatly enlarged. The most advanced lesions were seen in the terminal portion of the ileum, where numerous circumscribed, raised hemorrhagic nodules from 5 to 10 mm. in diameter were noted. They occurred most abundantly near the ileocecal valve. Some of the areas presented early necrotic changes. At the ileocecal junction were five hyperplastic, necrotic lymph nodules with crenated borders. Just within the ileocecal ring and in the cecum were a large hemorrhagic area and one necrotic lesion measuring 3 by 3 mm. The mucosa of the rectosigmoid presented a hemorrhagic appearance.

Cultures taken post mortem of the abdominal fluid, swabbings of the throat, heart blood, spinal fluid, feces and bone marrow yielded *Str. alpha* (viridans).

*Histopathologic Observations.*—Pulmonary edema was present, and many "heart failure" cells were noted. The parenchyma of the liver was the seat of

cloudy swelling, and the sinusoids were congested. The spleen exhibited congestion and edema of the splenic pulp with a suggestion of early formation of an infarct. In the kidneys bacterial emboli plugged the afferent vessels of some glomeruli, and many of the capillary tufts were blocked with bacteria. Many tubules were filled with similar clumps of organisms. One mesenteric node showed marked edema of the stroma with wide separation of the reticulum. The myocardium exhibited definite interfascicular edema.

*CASE 3.—History and Course.*—R. R., a boy aged 3 months, was admitted to the hospital on April 27, 1934, with a history of fretfulness and movement of the thighs suggestive of abdominal pain of four days' duration. For the preceding twenty-four hours distention was present. The temperature was 104 F.

On physical examination injected tonsils and pharynx, abdominal distention and rigidity were noted. Roentgenographic examination of the chest by Dr. Snow gave negative results, but the small intestine was distended with gas and exhibited fluid levels with the infant in the erect position suggesting obstruction in the small intestines.

Exploratory laparotomy seven hours after admission revealed distended intestines with free seropurulent fluid and flakes of fibrin in the peritoneal cavity. This was particularly evident about the ileocecal angle and appendix, where a thick, yellowish-green, plastic exudate was noted. Incision and drainage were done.

Following the operation the temperature remained at 105.2 F. The patient died four hours after the operation on the day of admission to the hospital and five days after the onset of the acute illness.

*Laboratory Data.*—The blood count on April 27 showed 24,500 leukocytes, with 6 per cent mature polymorphonuclears, 3 per cent young metamyelocytes, 54 per cent band forms, 35 per cent small lymphocytes and 2 per cent monocytes. A culture of the pus from the abdomen yielded *Str. alpha* (viridans).

*Postmortem Examination.*—The anatomic diagnosis was plastic peritonitis, perisplenitis, perihepatitis, mesenteric adenitis and multiple focal hemorrhagic lesions of the ileum and cecum.

The peritoneum was covered with a thick, yellowish, plastic exudate. The mesenteric lymph nodes were enlarged. The ileum appeared congested and exhibited many small focal hemorrhagic areas. The cecum showed similar lesions. The intestines were greatly distended with fluid feces and were matted together with a thick plastic exudate. The spleen and liver were covered with similar deposits. *Str. alpha* (viridans) was recovered from swabbings of the throat, abdominal fluid and heart blood.

*Histopathologic Observations.*—The pulmonary capillaries and arterioles were intensely congested, and an infarcted area was noted. The liver sinusoids were moderately congested. There were edema and hemorrhagic infiltration of the splenic pulp. The renal tissue exhibited acute hemorrhagic nephritis with swelling of the tubular parenchyma and endothelium of the capillary loops.

*CASE 4.—History and Course.*—S. M., a girl aged 2½ years, was admitted to the hospital on April 15, 1934, with a complaint of sore throat, abdominal pain, vomiting and fever. Seven days previously the patient had sore throat accompanied by general soreness and vomiting. The symptoms cleared up shortly, but four days later there was a recurrence in which abdominal pain was a prominent feature.

Physical examination disclosed an intensely reddened throat and tonsils which were covered with a punctate exudate. A nasal discharge was present. The entire abdomen was rigid and tender. The child looked acutely ill.

At operation by Dr. S. Colm on the day of admission to the hospital the abdomen was filled with a large amount of thick, creamy pus and large fibrinous clots. The appendix was inflamed by contiguity and covered with a purulent, plastic exudate. All the mesenteric lymph nodes were greatly enlarged. Appendectomy with drainage was performed.

The postoperative course was rapidly downhill. A mild convulsive seizure occurred on the day following the operation. Cyanosis of the arms and legs was noted. Death occurred on the second day of hospitalization, five days after the onset of acute abdominal symptoms and nine days after the first complaint of sore throat.

The temperature on the day of admission gradually rose from 102.8 to 104.4 F. with continued increase on the following day until 107.8 F. was reached shortly before death. The pulse rate varied between 144 and 164 and the respiratory rate from 48 to 90.

*Laboratory Data.*—The blood count on April 15 showed 32,400 leukocytes, with 95 per cent segmented forms. A culture of the pus from the abdomen yielded Str. alpha (viridans). Roentgenographic examination of the chest by Dr. Snow gave negative results.

The appendix was 4.5 cm. in length. The serosal vessels at the tip were injected, and the distal half of the canal was obliterated. Sections showed acute periappendicitis. There were also edema and congestion of the mucosa.

We were unable to secure consent for a postmortem examination, so the studies on animals were limited to those made with the peritoneal organism.

*CASE 5.—History and Course.*—E. B., a girl aged 8 years, was admitted to the hospital on Jan. 20, 1934, with a complaint of generalized abdominal pain which began abruptly eight hours previously and was unaccompanied by nausea or vomiting. On the day prior to admission the child complained of sore throat, and the condition was verified by the family physician, Dr. Rosenthal.

On admission the child appeared acutely ill. The tongue was coated and dry. The abdomen was rigid, and there was exquisite tenderness on light palpation in both lower quadrants.

Surgical intervention by Dr. J. Landy on the day of admission disclosed diffuse purulent peritonitis, most of the pus being situated in the pelvis. The appendix did not appear to be involved, but on opening it an irregular, superficial, oval ulcer was found in the mucosa extending down to the submucosal layer from which a drop of pus was expressed. There were two other well defined necrotic areas nearby. The postoperative course was very stormy. The abdomen became distended; the patient vomited greenish-yellow foul material repeatedly and was irrational. Two days after the first operation a jejunostomy was performed for paralytic ileus. A transfusion of 250 cc. of blood was given. The respirations became more shallow and of the Cheyne-Stokes type. The patient was in a state of profound shock and died on the fourth day of hospitalization, approximately four days after the onset of acute abdominal symptoms and five days after the angina was noted. It is of interest that on the second day postoperatively the child complained of pains in the joints, and held the neck rigid on being moved.

The temperature varied from 104 F. prior to admission to the hospital to 107 F. shortly before death. The pulse rate varied between 120 and 150.

*Laboratory Data.*—The leukocyte count on January 20 showed 18,000, with 90 per cent segmented forms. A culture of the peritoneal fluid revealed Str. alpha (viridans).

Permission for postmortem examination could not be obtained.

**CASE 6.—History and Course.**—M. C., a boy aged 6 months, was admitted to the hospital on March 8, 1934, with a history of a cough and inflamed throat for five days, during which the temperature fluctuated between 101.2 and 105 F. Eight hours before admission the family physician noted rigidity of the abdomen.

Physical examination revealed an infant acutely ill. The throat was congested, and cervical adenopathy was present. Edema of the scrotum and hydrocele were noted.

**Operation.**—A few hours after admission an abdominal paracentesis yielded seropurulent fluid which was cultured. On the following day a laparotomy was done by Dr. J. Landy, and free pus was found in the abdomen. Drainage was instituted, but the patient died on the second day of hospitalization, approximately three days after the onset of acute abdominal signs and one week after angina was noted. The temperature during hospitalization varied from 103.8 on admission to 105.8 F. shortly before death. The respiratory rate on the last day varied between 50 and 100. Abdominal distention, vomiting and twitching of the body were prominent features of the preoperative and postoperative periods.

**Laboratory Data.**—The blood count on March 7 showed hemoglobin, 70 per cent; erythrocytes, 3,750,000, and leukocytes, 14,000, with 22 per cent band forms and 60 per cent mature polymorphonuclears. The urine on March 7 contained albumin. A culture of the abdominal fluid on March 8 revealed *Streptococcus gamma* (non-hemolytic).

**Postmortem Examination.**—The anatomic diagnosis was generalized peritonitis, bronchopneumonia, edema of the scrotum and hydrocele.

The spleen and liver were covered with a thick, greenish-yellow purulent exudate. The intestines were matted together by the same material. The appendix appeared to be normal.

**Histopathologic Observations.**—Sections of pulmonary tissue showed bronchopneumonia with marked capillary and arteriolar congestion and hemorrhagic pleuritis. There was cloudy swelling with hydropic degeneration and fragmentation of the cords of the liver. The sinusoids were congested. Congestion of the splenic pulp and acute diffuse, nonhemorrhagic nephritis were present.

Cultures made of swabbings of the throat and heart and abdominal fluid were grossly contaminated, and the *Streptococcus* could no longer be recovered.

**CASE 7.—History and Course.**—M. L., a woman aged 29, was admitted to the hospital on March 10, 1934, in the first stage of labor. A history was obtained of sore throat at frequent intervals during the past month, the last attack having been one week before admission to the hospital. A Porro cesarean section was performed three days after admission. Culture from the uterus showed *Str. gamma* (non-hemolytic).

On the second day postoperatively signs of peritonitis were noted. The clinical course was rapidly downhill in spite of an emergency supracervical hysterectomy, and death occurred on the ninth day of hospitalization, six days postoperatively and thirteen days after a sore throat. Four transfusions, each of 350 cc. of blood, were given without avail.

It is noteworthy that on the first three days of hospitalization the temperature varied between 99 and 100.4 F. Five hours before the Porro cesarean operation, the patient had a chill and the temperature rose to 103.2 F. The postoperative temperature varied between 101 and 107 F., with an average of 106 F. during the three days preceding death.

**Laboratory Data.**—The blood count on March 17 showed hemoglobin, 66 per cent, erythrocytes, 3,700,000, and leukocytes, 18,400, with 24 per cent band forms

and 60 per cent mature polymorphonuclears. Two blood cultures were negative. The urine on March 17 contained albumin, erythrocytes and leukocytes.

*Postmortem Examination.*—The anatomic diagnosis was pelvic peritonitis, ulcerative colitis and proctitis, congested spleen, chronic adhesive pleurisy, bilateral, and acute metritis.

Pelvic peritonitis was fairly well localized to the surgical field. No vascular thrombosis or phlebitis was noted. Some of the loops of the small intestine were adherent and covered with necrotic, grayish purulent membrane. In the region of the sigmoid flexure and rectum were seen many ulcerated areas on the mucosa.

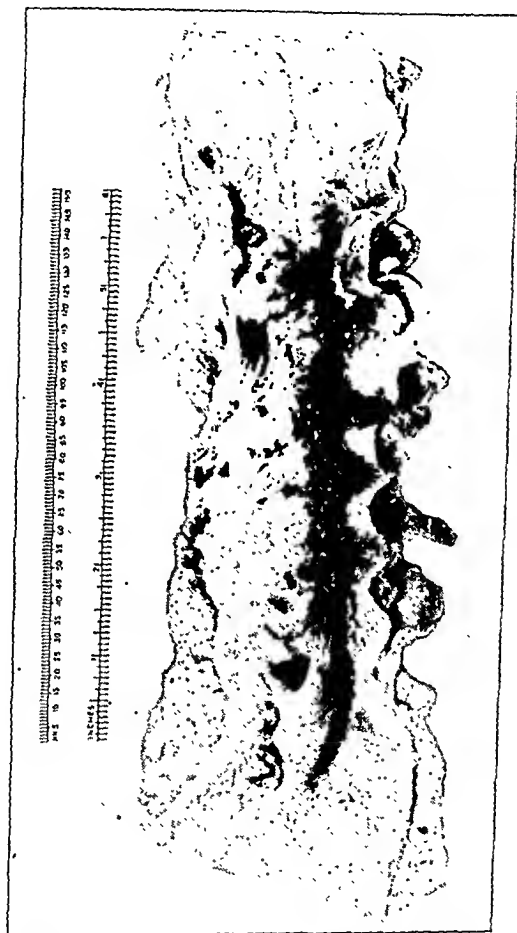


Fig. 3 (case 7).—Multiple focal areas of necrosis in the intestine.

These were shallow, from 2 to 3 cm. in diameter, circular and surrounded by a greenish fringe of purulent membrane which could not readily be removed. The peritoneal organism was a nonhemolytic streptococcus.

*Histopathologic Observations.*—The sinusoids of the liver were moderately congested. A splenic infarct was present. The renal tissue showed acute hemorrhagic nephritis with thrombi in some of the smaller arterioles. The myocardium exhibited interfascicular edema and some fibrosis. The vessels in the ovary were congested, and the uterus gave evidence of acute metritis which appeared to start from the peritoneal aspect in the region of the operative wound.

CASE 8.—*History and Course*.—E. F., a woman aged 34, was admitted to the hospital on March 2, 1934, with a complaint of diffuse abdominal pain and nausea of two days' duration. The temperature varied between 104 and 105 F. On the day of admission the pain became more intense and appeared to be localized to the lower portion of the abdomen. The patient had had sore throat approximately one week before admission. She appeared to be acutely ill. The entire abdomen was rigid, and tenderness was most marked in the right lower quadrant.

Surgical intervention by Dr. Amster on the day of admission disclosed free pus in the abdomen. The omentum was wrapped around the cecum and adjoining loops of small bowel. The appendix appeared to be normal. The postoperative course was stormy. The patient was delirious, complained of dysphagia and died on March 6, approximately two weeks after an attack of sore throat and six days after the onset of acute abdominal symptoms.

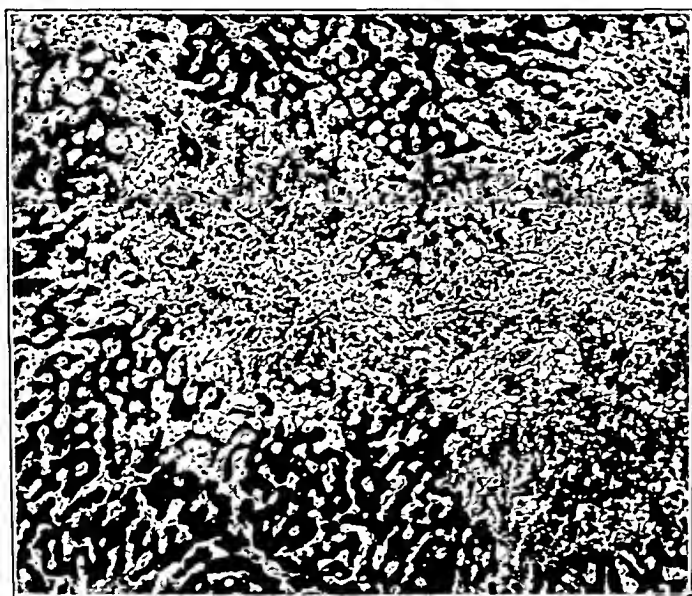


Fig. 4 (case 8).—Photomicrograph of multiple necrotic lesions of the parenchyma of the liver.

The temperature on admission was 105.2 F. and averaged 104 F. during the entire period of hospitalization. The pulse rate varied from 120 to 144 and the respiratory rate from 26 to 42.

*Laboratory Data*.—The leukocyte count on March 3 showed 47,000, with 83 per cent segmented polymorphonuclears, 15 per cent band forms and 2 per cent lymphocytes. The urine on March 3 and 5 contained albumin and some leukocytes. A culture of the abdominal pus yielded *Str. gamma* (nonhemolytic).

The appendix was 5 cm. in length and was covered with a thin fibrinous exudate. The sections showed early acute periappendicitis.

*Postmortem Examination*.—The anatomic diagnosis was generalized peritonitis, splenic infarcts, renal abscess and pleurisy on the right side.

The peritoneal cavity was filled with a plastic purulent exudate and a thinner purulent fluid. Recent fibrinous adhesions were seen everywhere, particularly in



the cecal and sigmoid regions. The loops of intestine were matted together. Perihepatitis and perisplenitis were noted. There was no localized formation of abscess, and the subphrenic spaces were clear. The right kidney exhibited a cortical abscess the size of a pinhead. The stomach was greatly distended and covered with a purulent exudate. There was moderate enlargement of the mesenteric nodes. Both lungs were congested at the base, and the right pleura was covered with a purulent membrane.

*Histopathologic Observations.*—Sections of pulmonary tissue showed intense vascular congestion and edema. In the liver were scattered areas of hydropic degeneration, chiefly at the periphery of the lobules, and the sinusoids were congested. There were edema, congestion and hyaline thrombi in the splenic pulp. The vessels in the wall of the fallopian tube were intensely congested.

TABLE 1.—*Results of Inoculation of Rabbits with Organisms Recovered from the Patient in Case 1*

Rab- bit	Source of Str. Viridans	Dosage, Cc.	Days	Result	Histopathologic Observations
5	Peritoneum	(1) 3	4	Organism recovered from feces; diarrhea	Focal necroses in liver
		(2) 6 (13th day)	1	Positive blood culture	
		(3) 6 (23d day)	4	Positive blood culture	
			6	Fatal; organism recovered from pericardial sac, peri- toneum and heart blood	
99	Peritoneum	3	8	Killed; necrotic lesions in ileum; organism re- covered from feces	Intestinal lymphoid hyperplasia with cen- tral necrosis of soli- tary nodules
66	Peritoneum	3	2	Killed; superficial ulcers in ileum	
28	Peritoneum	7: toxin	..	No effect	

#### STUDIES IN ANIMALS

In the studies on animals certain objectives were kept in mind in each experiment which are indicated in the protocols. Preliminary control tests were made on each animal before inoculation. Eighteen hour broth cultures and the intravenous route were used except when otherwise specified.

CASE 1.—The organism recovered from the peritoneal fluid was used.

*Rabbit 5.*—Three cubic centimeters of an eighteen hour broth culture was injected. The organism was recovered from the feces on the fourth day when slight diarrhea was noted. On the thirteenth day a second inoculation of 6 cc. was made. Twenty-four hours later the blood culture was positive. The rabbit survived, and on the twenty-third day a third inoculation of 6 cc. was made. After four days the blood culture was positive, and the animal died two days later. Postmortem examination revealed that the pericardial sac contained 25 cc. of flaky, purulent exudate, the abdomen was filled with 40 cc. of blood-tinged, flaky, purulent exudate most evident in the hepatic and splenic areas, and the liver was dark red and congested. The organism which had been injected was recovered from the pericardial sac, peritoneal cavity and heart blood. Sections of the liver showed multiple focal necroses most marked in the lobules nearest the capsule. The sinusoids were dilated with clear fluid. The spleen exhibited edema of the pulp.

*Rabbit 99.*—Three cubic centimeters of a broth culture was injected intravenously. The animal was killed eight days later. Small necrotic areas were found in the ileum. The organism which had been injected was recovered from the feces. Sections of the intestine showed marked lymphoid hyperplasia with small areas of central necrosis in the solitary nodules.

*Rabbit 66.*—Three cubic centimeters of a broth culture was injected intravenously. Slight diarrhea was noted, and the animal was killed after forty-eight hours. A few superficial ulcer-like erosions were noted in the ileum.

TABLE 2.—*Results of Inoculation of Rabbits with Organisms Recovered from the Patient in Case 2*

Rabbit	Source of Str. Viridans	Dosage, Cc.	Days	Result	Histopathologic Observations
72	Throat	5: intravenously	2	Organism recovered from feces; survived	
48	Peritoneum	7: orally	7	Organism recovered from feces; survived	
57	Peritoneum	13: by rectum	7	Organism recovered from feces; survived	
19	Peritoneum	4: toxin intravenously	21	Diarrhea; congestion of small intestines	Portal congestion of liver
39	Peritoneum	5: intravenously	5	Diarrhea; fatal; organism recovered from throat, feces, peritoneum, spleen, liver, spinal fluid, pericardial fluid; ulcerative and hemorrhagic lesions in ileum and appendix; purulent pericarditis; peritonitis	Lymphoid hyperplasia with slight central necrosis
30	Heart blood	5: intravenously	5 15	Diarrhea Fatal; organism recovered from throat, peritoneum, pericardium, liver, spleen, feces, spinal fluid and heart blood; purulent peritonitis; pericarditis; perihepatitis	Pulmonary edema; hemorrhagic pleuritis, focal necroses in liver
65	Feces	6: intravenously	6	Fatal; organism recovered from throat, peritoneum, pericardium, liver, spleen, feces, spinal fluid and heart blood; purulent peritonitis; pericarditis	
98	Spinal fluid	8: intravenously	12	Fatal; organism recovered from throat, peritoneum, pericardium, liver, spleen, feces, spinal fluid and heart blood; fibrinous pericarditis and peritonitis; focal hemorrhagic enterocolitis	

*Rabbit 28.*—Seven cubic centimeters of toxin (filtered eighteen hour broth culture) was injected with no untoward results.

CASE 2.—*Rabbit 72.*—The organism from the throat of the patient, in 8 cc. of bouillon culture, was injected intravenously. Forty-eight hours and four days later the organism was recovered from the feces.

*Rabbit 48.*—The peritoneal organism, in 7 cc. of bouillon culture, was administered orally. The organism was recovered in the feces one week later. The animal survived.

*Rabbit 57.*—The peritoneal organism, in 13 cc. of bouillon culture, was given by rectum. The organism was recovered from the feces one week later. The animal survived.

*Rabbit 19.*—Four cubic centimeters of the toxin of the peritoneal organism (eighteen-hour filtered broth culture) was injected intravenously. Mild diarrhea ensued. The animal was killed after twenty-one days, and congestion of the small intestines was noted. Sections of the liver showed moderate portal congestion, but no essential pathologic change.

*Rabbit 39.*—The peritoneal organism, in 8 cc. of bouillon culture, was injected intravenously. Diarrhea was noted, and death occurred in five days. The organism was recovered from the throat, feces, peritoneum, spleen, liver, spinal fluid and pericardial fluid. Early ulcerative lesions were noted in the

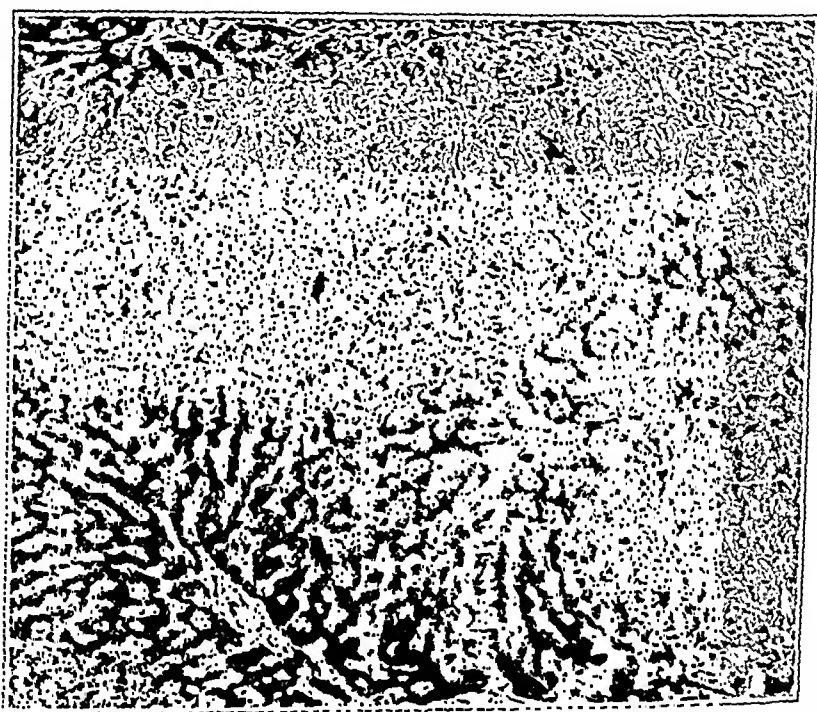


Fig. 5 (rabbit 30, inoculated with peritoneal organism from the patient in case 2).—Photomicrograph of multiple necrotic lesions of the parenchyma of the liver.

ileum and punctate hemorrhagic areas in the ileum and appendix. Purulent pericarditis and peritonitis were present. Sections of the intestine showed lymphoid hyperplasia and an enlarged mesenteric node with slight central necrosis.

*Rabbit 30.*—The organism recovered from heart blood, in 5 cc. of bouillon culture, was injected intravenously. At the end of the fifth day diarrhea was evident, and the rabbit appeared sickly. Profuse diarrhea followed, and the animal died on the fifteenth day. The organism was recovered from the throat, peritoneal fluid, pericardial fluid, liver, spleen, feces, spinal fluid and heart blood. Seropurulent fibrinous peritonitis, pericarditis and profuse purulent perihepatitis were noted. Sections of tissue of the lungs showed pulmonary edema and hemorrhagic pleuritis. In the liver were small focal necroses, most marked in the lobules nearest the capsule. In the spleen were focal areas of large macrophages laden with blood pigment.

*Rabbit 65.*—The organism from the feces, 6 cc. of bouillon culture, was administered intravenously. Death occurred in six days. The organism was recovered from the throat, peritoneal fluid, pericardial fluid, liver, spleen, feces, spinal fluid and heart blood. Seropurulent fibrinous pericarditis and peritonitis were present. The spleen was markedly congested.

*Rabbit 98.*—The organism from the spinal fluid, 8 cc. of bouillon culture, was injected intravenously. Death occurred in twelve days. The organism was recovered from the throat, peritoneal fluid, pericardial fluid, liver, spleen, feces, spinal fluid and heart blood. There were fibrinous peritonitis and

TABLE 3.—*Results of Inoculation of Rabbits with Organisms Recovered from the Patient in Case 3*

Rab-bit	Source of Str. Viridans	Dosage, Cc.	Days	Result	Histopathologic Observations
17	Peritoneum	5: intravenously	3	Diarrhea; positive blood culture; organism recovered from feces	Lymphoid hyperplasia of mesenteric node with focal hemorrhagic areas
			5	Fatal; organism recovered from blood, feces and peritoneum; hemorrhages in terminal ileum	
50	Peritoneum	5: toxin intravenously	..	No effect	
		8: intravenously	18 hrs.	Diarrhea; fatal; organism recovered from throat, peritoneum, pericardium, feces, spleen and heart blood	
46	Throat	(1) 5: intravenously	1	Organism recovered from feces	
			3	Positive blood culture	
			7	Positive blood culture	
		(2) 6: intravenously (8th day)	1	Organism recovered from feces	
		(3) 8: intravenously (27th day)		Survived	
64	Throat	8: intravenously	2	Organism recovered from feces; survived	
25	Heart blood	5: intravenously	1	Organism recovered from feces	Areas of coagulation necrosis in liver; splenic infarct; hemorrhagic nephritis
			3	Fatal; organism recovered from blood, feces; ulcers in terminal ileum	

pericarditis and free fluid in the pericardium. The intestinal tract was greatly distended and injected. Focal hemorrhagic areas were noted in the small and large intestines. The kidneys appeared to be granular and edematous. Small whitish necrotic areas were seen in the auricles. Sections of the liver showed marked congestion of the central veins and sinusoids. The walls of some vessels were composed entirely of a thick, structureless, hyaline material suggestive of a degenerative or necrotic lesion. The splenic pulp was infiltrated with blood, and many macrophages loaded with blood pigment were present. The intestinal section showed a single thrombosed vessel.

*CASE 3.—Rabbit 17.*—The peritoneal organism, in 5 cc. of a bouillon culture, was given intravenously. Three days later the blood culture was positive, and the organism was recovered from the feces. Diarrhea appeared and increased until the rabbit died five days after the injection. The organism was recovered from the blood, feces and peritoneum. There was a diffuse fine hemorrhagic

speckling of the terminal ileum. Sections of the intestine exhibited no noteworthy pathologic change, but a mesenteric node showed lymphoid hyperplasia with marked edema and focal hemorrhagic areas.

*Rabbit 59.*—Five cubic centimeters of toxin (filtered eighteen hour broth culture) of the peritoneal organism was given intravenously without effect. The



Fig. 6 (rabbit 17, inoculated with peritoneal organism from patient in case 3).—Multiple focal hemorrhagic areas of necrosis in the intestine.

animal was reinoculated with 8 cc. of a bouillon culture intravenously. Profuse diarrhea ensued, and death occurred in eighteen hours. Postmortem examination revealed a sanguinopurulent exudate in the peritoneal cavity; the intestines were distended, and the spleen appeared congested. Positive cultures were obtained from the throat, peritoneum, pericardium, feces, spleen and heart blood.

*Rabbit 46.*—The organism from the throat, in 5 cc. of a bouillon culture, was given intravenously. The following day the organism was recovered from the feces. On the third and the seventh day the blood cultures were positive. A second inoculation of 6 cc. was given on the eighth day. The organism was again recovered from the feces. On the twenty-seventh day a third inoculation of 8 cc. was given. The animal survived.

*Rabbit 64.*—The organism from the throat, in 8 cc. of bouillon culture, was injected intravenously. The organism was recovered from the feces two days later. The animal survived.

*Rabbit 25.*—The organism from heart blood, in 5 cc. of bouillon culture, was injected intravenously. On the following day the organism was recovered from the feces. Death occurred on the third day, and the organism was recovered from the blood, feces and ulcerated lesions in the terminal ileum. Sections of the liver showed small areas of coagulation necrosis about the central veins and near the

TABLE 4.—*Results of Inoculation of Rabbits with Organisms Recovered from the Patient in Case 4*

Rab- bit	Source of Str. Viridans	Dosage, Cc.	Days	Result	Histopathologic Observations
34	Peritoneum	6: intravenously	2	Fatal; peritonitis; pericarditis; congestion of lungs; organism recovered from throat, peritoneum, pericardium, liver, spleen, heart blood, spinal fluid and feces	Diffuse parenchymatous degeneration of liver; multiple glomerular bacterial emboli kidney (same as in case 2)
96	Peritoneum	8: intravenously	2	Profuse diarrhea; fatal; fibrinous peritonitis; pericarditis; congested spleen; organism recovered from throat, peritoneum, pericardium, liver, spleen, heart blood, spinal fluid and feces	

capsule. In the splenic pulp were extensive hyaline thrombi with infarction. There was acute hemorrhagic nephritis with massive hemorrhages, shrunken glomeruli and parenchymatous degeneration.

*CASE 4.—Rabbit 34.*—The organism, in 6 cc. of broth culture, was injected intravenously. Death occurred in two days. The intestinal tract was greatly distended, and a small amount of free serosanguineous fluid was seen in the peritoneal cavity. There was a fibrinous exudate over the liver and the entire visceral and parietal peritoneum. A similar exudate was present in the pericardial sac. The lungs were congested. The organism was recovered from the throat, peritoneum, pericardium, liver, spleen, heart blood, spinal fluid and feces. Sections of the liver showed diffuse parenchymatous degeneration with clumps of bacteria in the sinusoids. There was cloudy swelling of the renal parenchyma with multiple glomerular bacterial emboli.

*Rabbit 96.*—The organism, in 8 cc. of broth culture, was given intravenously. Profuse diarrhea occurred, and death ensued in two days. The peritoneum was covered with a thin fibrinous exudate and the peritoneal cavity contained 10 cc. of serosanguineous fluid. The large intestine was greatly distended. The spleen was enlarged and congested. There was a thin fibrinous exudate in the pericardial sac. The organism was recovered from the throat, peritoneum, pericardium, liver,

spleen, heart blood, spinal fluid and feces. Sections of the liver showed diffuse parenchymatous degeneration. There were moderate congestion and edema of the splenic pulp.

#### IMMUNOLOGIC STUDIES

Having determined that the various strains of *Str. viridans* contained many similar features in their action on the animal host, we questioned the possibility of an antigenic similarity among all the strains. We felt that if this identity in antigenic structure could be demonstrated we might dispel such objections as coincidental finding of *Str. viridans* in a few cases, agonal infection or extraneous contamination.

If a serum containing antibodies to one of the strains would unite specifically with the other antigens this similarity in antigenic structure

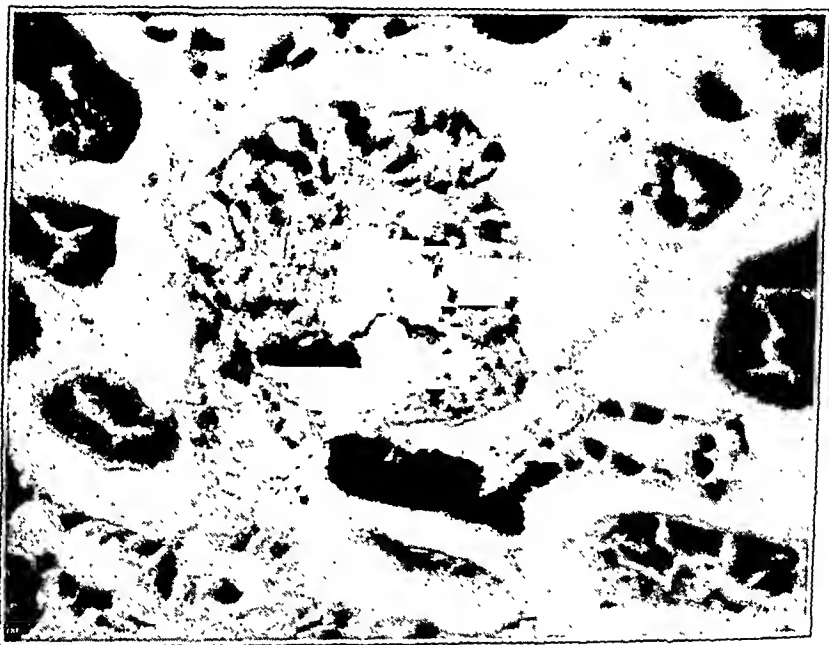


Fig. 7 (rabbit 34, inoculated with peritoneal organism from the patient in case 4).—Photomicrograph of a bacterial embolus in a glomerulus and afferent vessel.

would be established. We chose the complement-fixation test for this purpose because of its great sensitivity.

The actual experiment was conducted according to the protocol, and the reagents which were used were prepared as follows:

*Complement.*—Fresh guinea-pig serum was used. The titration was performed so that in a suitable dilution of the serum, 0.2 cc. contained 2 units.

*Antigen.*—The various antigens used are listed in table 6. They consisted of eighteen hour serum broth ( $pH$  7.8) cultures of the desired organism. In preliminary tests the anticomplemental action and hemolytic power of each antigen were titrated. It was found that 0.2 cc. of a 1:5 dilution of the culture in saline solution did not inhibit the action of the complement and was not hemolytic for the sheep cells.

TABLE 5.—Clinical and Pathologic Observations on Eight Cases and Results of Experimentation on Animals in Four Cases

Case and Age	No. of Days Between Onset of Angina and Symptoms	No. of Days Between Onset of Acute Abdominal Symptoms and Death	Temperature (Peak, F.)	Count on Adm.-scoop*	Organism	Animal Studies			
						Gross Pathologic Observations	Histopathology	Organism Recovered From	Illstopathology
1 23 yr.	7 days	7 days	107.6	15,000 35	Str. viridans	Peritonitis; periaependicitis and colitis; hemorrhagic inflammation of the intestines, liver, spleen, kidneys, ovaries and lungs	Pulmonary congestion; degeneration of the liver; hyaline thrombi in the spleen; hemorrhagic nephritis; oophoritis	Peritonium	Infestinal lymphoid hyperplasia; focal necroses in the liver
2 1½ yr.	7 days	1 days	105.6	30,000 80	Str. viridans	Peritonitis; periaependicitis; mesenteric adenitis; hemorrhagic enterocolitis; perisplenitis; bronchopneumonia	Pulmonary edema; degeneration of the liver; splenic infarct; emboli in the kidneys; mesenteric adenitis; myocarditis	Peritonium, throat, blood, splenic fluid, feces, bone marrow	Ulcervative and hemorrhagic lesions in the ileum and appendix; mesenteric adenitis; vascular necrosis and thrombosis; pulmonary edema; hemorrhagic pleuritis; focal necroses in the liver
3 3½ mo. admission	5 days	5 days	105.2	21,500 51 band forms	Str. viridans	Peritonitis; periaependicitis; mesenteric adenitis; focal hemorrhagic lesions in the ileum and perihepatitis	Pulmonary infarct; congestion of the spleen; hemorrhagic hepatitis	Throat, peritonium, blood	Focal hemorrhagic mesenteric adenitis; necroses in the liver; splenic infarct; hemorrhagic nephritis
4 2½ yr.	5 days	5 days	107.8	32,400 95	Str. viridans	Peritonitis; periaependicitis; mesenteric adenitis (no autopsy)	Periaependicitis; mesenteric adenitis	Peritonium	Degeneration of the liver; emboli in the kidneys
5 8 yr.	1 day	4 days	107.0	18,000 90	Str. viridans	Peritonitis; periaependicitis with superficial ulcerative appendicitis; paralytic ileus; arthritis (?); mesenteric adenitis (no autopsy)	.....	Appendix, peritonium	
6 6 mo.	1 days	3 days	105.8	11,000 22 band forms; 60 P.N.	Nonhemolytic streptococcus	Peritonitis; periaependicitis; edema of the serotum; hydrocele; perisplenitis; perihepatitis; bronchopneumonia	Bronchopneumonia; hemorrhagic pleuritis; degeneration of the liver; congestion of the spleen; acute nephritis	Peritonium	
7 2½ yr.	0 days	4 days	107.0	18,400 21 band forms; 60 P.N.	Nonhemolytic streptococcus	Peritonitis; ulcerative colitis; congested spleen	Congestion of the liver; splenic infarct; acute hemorrhagic nephritis; myocarditis; acute metritis	Peritonium, uterine wound	
8 31 yr.	8 days	6 days	105.0	47,000 83 band forms; 15 P.N.	Nonhemolytic streptococcus	Peritonitis; periaependicitis; splenic infarct; renal abscess; pleurisy	Pulmonary congestion; degeneration of the liver; splenic infarct; congestion of a fallopian tube	Peritonium	

\* 15,000

—85 refers to the total leukocyte count over the percentage of polymorphonuclears.

† This count was made two days before death.

When Sedling counts were made the percentage of band forms is stated. P. N. refers to



*Serum.*—The serum was obtained by bleeding rabbits 26 and 46. These rabbits successfully withstood three large injections of the streptococcus. It seemed likely, then, that the serum of rabbit 26 contained antibodies to the organism isolated from the abdominal fluid of the patient in case 1 and that the serum of rabbit 46 similarly contained antibodies to the organism isolated from the throat of the patient in case 3. The serum of each rabbit was titrated for anticomplemental action and hemolytic power. Here, too, we found that 0.2 cc. of a 1:5 dilution of the serum contained 2 units.

*Saline Solution.*—Fresh solutions of 0.85 per cent sodium chloride were used for all dilutions.

TABLE 6.—*Protocol of Complement-Fixation Tests Showing Antigenic Similarity of Ten Strains of Str. Viridans Isolated in Cases 1, 2, 3 and 4*

Tube	Case	Antigen	Serum		Comple- ment, Cc.	Saline Solution, Cc.	Sensitized Cells, Cc.	Lysis
			Rabbit	Cc.				
1	1	Abdominal fluid	26	0.2	0.2	0	0.4	0
2		0.2 cc.	46	0.2	0.2	0	0.4	++++
3		0.2 cc.	0	0	0.2	0.2	0.4	++++
4	2	Peritoneum	26	0.2	0.2	0	0.4	0
5		0.2 cc.	46	0.2	0.2	0	0.4	+++
6		0.2 cc.	0	0	0.2	0.2	0.4	++++
7	2	Throat	26	0.2	0.2	0	0.4	0
8		0.2 cc.	46	0.2	0.2	0	0.4	+++
9		0.2 cc.	0	0	0.2	0.2	0.4	++++
10	2	Heart blood	26	0.2	0.2	0	0.4	0
11		0.2 cc.	46	0.2	0.2	0	0.4	+++
12		0.2 cc.	0	0	0.2	0.2	0.4	++++
13	2	Abdominal fluid	26	0.2	0.2	0	0.4	0
14		0.2 cc.	46	0.2	0.2	0	0.4	+++
15		0.2 cc.	0	0	0.2	0.2	0.4	++++
16	2	Spinal fluid	26	0.2	0.2	0	0.4	0
17		0.2 cc.	46	0.2	0.2	0	0.4	+++
18		0.2 cc.	0	0	0.2	0.2	0.4	++++
19	3	Throat	26	0.2	0.2	0	0.4	0
20		0.2 cc.	0	0	0.2	0.2	0.4	+++
21		0.2 cc.	46	0.2	0.2	0	0.4	0
22	3	Heart blood	26	0.2	0.2	0	0.4	0
23		0.2 cc.	46	0.2	0.2	0	0.4	++++
24		0.2 cc.	0	0	0.2	0.2	0.4	++++
25	3	Abdominal fluid	26	0.2	0.2	0	0.4	0
26		0.2 cc.	46	0.2	0.2	0	0.4	+++
27		0.2 cc.	0	0	0.2	0.2	0.4	++++
28	4	Abdominal fluid	26	0.2	0.2	0	0.4	0
29		0.2 cc.	46	0.2	0.2	0	0.4	+++
30		0.2 cc.	0	0	0.2	0.2	0.4	++++
31	0		46	0.2	0.2	0.2	0.4	++++
32	0		26	0.2	0.2	0.2	0.4	++++
33	0		0	0	0.2	0.4	0.4	++++
34	0		0	0	0	0.6	0.4	0

*Sensitized Cells.*—The sensitizer (amboceptor) was titrated in the usual manner and was used so that at the desired dilution 0.2 cc. contained 2 units. Sheep cells washed free from the serum and packed after the final washing were used in a 5 per cent suspension. Equal volumes of the diluted sheep cells and the sensitizer were mixed. After the mixture had stood for at least half an hour it was considered suitable for use.

The antigen, complement and serum were placed in the tubes according to table 6, and the tubes were kept at 37.5 C. for half an hour. The sensitized cells were then added, and the tubes were replaced in the water bath for fifteen minutes. Throughout the test the tubes were shaken frequently. Readings were taken as soon as the test was completed and after the tubes had been in the refrigerator overnight. There was but slight variation in the two readings. Complete hemol-

ysis or lack of inhibition is represented in table 6 by ++++. Complete inhibition or lack of hemolysis is represented by 0.

The test as finally recorded shows that every strain used was able to inhibit lysis with the serum of rabbit 26. Although this rabbit was inoculated with the organism isolated from the abdominal fluid of the patient in case 1, it had antibodies which reacted with all the other strains. The uniform results with this serum showed that the various strains of *Streptococcus viridans* unquestionably contain a similar antigen. The possibility that the antigenic structure of the various strains is similar cannot be vouchsafed from this test alone.

The foregoing conclusion was partly confirmed by the action of the serum from rabbit 46. The definite but variable inhibition which was obtained with this serum was probably due to the absence of antibodies in any great amount. Although this serum gave complete inhibition with its own strain (tube 21), it gave only partial, and in most cases only slight, inhibition with the other strains.

This fact might argue against the identical antigenic structure of each strain, but it shows that in any case there is present in all of these organisms at least one common antigenic feature.

#### CORRELATION OF DATA

In all the eight patients studied there was a definite antecedent history of sore throat. The average period which elapsed between the angina and the onset of acute abdominal symptoms was five and eight-tenths days. The average duration of the disease from the time abdominal symptoms were noted until death was four and seven-tenths days. In each instance the onset was abrupt. In three cases (1, 7 and 8) the condition of the throat had cleared up prior to the development of peritonitis. In case 4 the angina improved and then recurred and was followed by peritonitis. The tendency to seasonal incidence is indicated by the fact that four of the eight reported cases occurred in a period of eight days, from March 2 to March 10. Search of the hospital records reveals only one other case of so-called primary peritonitis since 1917, and the patient in that case was admitted to the hospital on March 17, 1927. The diagnosis was confirmed at operation by Dr. A. A. Berg. There was an antecedent history of sore throat, a hemolytic streptococcus was obtained from the peritoneum, and the patient recovered.

Three adults and five children were affected. There appeared to be no essential difference in the clinical aspects of the disease in the two age groups. In the case of two of the adults the organism was nonhemolytic, but the general features were the same with both the viridans (five cases) and the nonhemolytic type (three cases). Extremely high temperatures were seen in both groups (from 107 to 107.8 F.). Vomiting was a prominent feature in four cases, but diarrhea was noted in only one (case 2), in which profuse watery stools were present throughout the period of hospitalization. Paralytic ileus occurred in two cases and epistaxis in one.

The organism recovered from the peritoneum was found elsewhere when it was sought. Thus, in case 2 the identical strain was found in

the throat, peritoneum, blood, feces, spinal fluid and bone marrow. In case 3 the organism was recovered from the throat, peritoneum and blood. It is noteworthy that acute arthritis was present in case 5, in which the causative organism was *Str. viridans*. Convulsions occurred in case 4, which may be significant in view of the fact that in the studies on animals the organism from the patient was recovered in the spinal fluid.

The initial leukocyte count was high, the general level being higher in the children than in the adults. The Schilling counts indicated active response of the marrow, the band forms in one instance (case 8) being 83 per cent of a total leukocyte count of 47,000. In case 1 there was a fall in the number of leukocytes from 15,000 on admission to the hospital to 8,600 two days before death.

The pathologic picture in each case was essentially that of streptococcic septicemia with profound toxic effects. Formation of multiple abscesses was not seen as in cases of staphylococcic septicemia. The disease process appeared to be too rapid and the causative organism too potent to permit of any localized formation of abscesses. The lesions were most evident in the lungs, liver, spleen, intestine, mesenteric nodes and kidneys. The histopathologic pictures in general were congestive or hemorrhagic owing to a toxic effect on the walls of the smaller vessels. Bacterial emboli were noted in the glomerular vessels in case 2. Splenic infarcts were present in three of the six cases in which a post-mortem examination was carried out, and a pulmonary infarct was noted in a third case. The intestinal lesions were essentially focal, hemorrhagic, necrotic areas which were seen as dark red, slightly raised, round or oval areas with a well defined outline just beneath the mucosa. They were most numerous in the small intestine, particularly in the terminal portion of the ileum, and were generally accompanied by mesenteric adenitis. The microscopic picture was that of coagulation or liquefactive necrosis which was limited to the vascular submucosa and appeared to represent an effect on the wall of the vessel rather than an embolic phenomenon. Superficial nonhemorrhagic, necrotic and deeper ulcerative lesions were also noted in both the small and the large intestines. These intestinal lesions were clearcut in four of the six cases in which autopsy was performed. Aside from the intestine the toxic effects were most apparent in the liver, spleen, kidneys and lungs.

The studies in animals almost duplicated the general picture seen in the human patients clinically, pathologically and bacteriologically. The disease was produced with an unusual degree of constancy and did not depend on lowering the resistance of the animals, introduction of foreign bodies into the peritoneal cavity or mechanical injury. The frequency of pericardial involvement in the animals should be noted. Bacterial

embolism of the glomerular tufts seen in sections of the kidney in case 2 was also seen in rabbit 34.

Many of the clinical features noted in our studies have been described by other investigators. The antecedent angina has been stressed by Nordlund,<sup>1</sup> who reported a large series of cases which were analyzed chiefly from the clinical standpoint. Schwartz,<sup>2</sup> Lipschutz and Lowenburg,<sup>3</sup> Ransohoff and Greenebaum,<sup>4</sup> Girgensohn<sup>5</sup> and de la Chapelle<sup>6</sup> have stressed the focal infection in the throat, particularly in children, and the organism in each case reported was a hemolytic streptococcus. Davis and Rosenow<sup>7</sup> reported an epidemic of sore throat due to a streptococcus which resembled that caused by both the hemolytic and the viridans type. The clinical features were a sudden aggravation of symptoms after from seven to ten days with the development of septicemia. Positive blood cultures were obtained only when the lymph nodes were not involved. Peritonitis, arthritis and meningitis were some of the complications, and the organism was isolated from the throat as well as from the secondary lesions. On postmortem examination in four cases an acute serofibrinous peritonitis was revealed from which a pure culture of streptococci was obtained. In three instances acute fibrinous pleurisy was present, and the organism was present in the heart blood. One patient had acute pericarditis. The close similarity of these cases to ours as well as to the disease in animals is noteworthy.

In most of the reported cases a hemolytic streptococcus was isolated. Our group is exceptional, therefore, since in five cases there were the viridans and in three the nonhemolytic type. We would not, however, stress this point unduly, as technical difficulties may account for the strict differentiation of the alpha, beta and gamma organisms.

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1. Nordlund, U.: Ueber die sogenannte primäre kryptogenetische oder metastatisch Streptokokkenperitonitis: Akademische Abhandlung, reprinted from Ann. Acad. Sc. Fennicae, ser. A., vol. 38, no. 1, Helsinki, 1933.

2. Schwartz, J.: Primary Streptococcus Peritonitis in Children, Surg., Gynec. & Obst. **45**:590, 1927.

3. Lipschutz, B., and Lowenburg, H.: Pneumococcic and Streptococcic Peritonitis, J. A. M. A. **86**:99 (Jan. 9) 1926.

4. Ransohoff, J. L., and Greenebaum, J. V.: Acute Hematogenous Streptococcic Peritonitis in Children, Arch. Pediat. **42**:315, 1925.

5. Girgensohn, R.: Ueber metastatische Peritonitis, Arch. f. klin. Chir. **141**: 196, 1926.

6. de la Chapelle, A.: Beitrag zur Kenntnis der sogenannten primären akuten Streptokokkenperitonitiden mit besonderer Berücksichtigung ihrer Beziehungen zur Angina tonsillaris, Arb. a. d. path. Inst. zu Helsingfors **2**:583, 1908.

7. Davis, D. J., and Rosenow, E. C.: An Epidemic of Sore Throat Due to a Peculiar Streptococcus, J. A. M. A. **58**:773 (March 16) 1912.

The early appearance of diarrhea, almost universally noted by other authors, was peculiarly absent in almost all of our cases and in Ziergold's<sup>8</sup> group.

Although a high incidence of positive blood cultures has been reported by a few authors, notably Duncan,<sup>9</sup> the general opinion is that during life the bacteremia is rather transient and positive blood cultures are most likely to be obtained early in the disease. The reason probably lies in the bactericidal power of the blood and the irregular and sparse feeding of organisms from the primary focus. Clinically this appears to be supported by the observation that in three of our cases the angina had completely cleared up before the onset of abdominal symptoms. Rabinowitz<sup>10</sup> reported an average interval of from three to four days between the onset of symptoms in the throat and in the abdomen.

The mortality in metastatic streptococcic peritonitis has been uniformly high. Nordlund reported survival in 5.3 per cent of the cases, death within two days after the onset of abdominal symptoms in 22.8 per cent and death within from four to seven days in 42.1 per cent. Our average period of survival was four and seven-tenths days and the mortality 100 per cent, a surprising thing in view of the fact that in no case was the organism of the hemolytic type, which is generally conceded by clinicians to be the most virulent. An isolated case of recovery, such as the one mentioned previously from our records, has been reported for the hemolytic streptococcic type by MacLennan and McNee.<sup>11</sup>

The experimental work on metastatic streptococcic peritonitis has been noteworthy by the lack of success in producing the disease by feeding or inoculation except when the injections were made directly into the peritoneal cavity after preliminary injury or in conjunction with some foreign necrotic material (Behrendt,<sup>12</sup> Wegner,<sup>13</sup> Pawlowsky,<sup>14</sup> Steinberg and Ecker<sup>15</sup>). We reproduced the disease consistently in most of our animals by the intravenous injection of eighteen-hour broth cultures. The ease with which we did this, even with some old cultures, suggests the possibility of a selective affinity of our strains

8. Ziergold, A. A.: Primary Peritonitis, *Ann. Surg.* **79**:418, 1924.

9. Duncan, J. H.: *Canad. M. A. J.* **24**:778 (June) 1931.

10. Rabinowitz, M. A.: Acute Hematogeneous Streptococcic Peritonitis, *Am. J. M. Sc.* **157**:797, 1919.

11. MacLennan, A., and McNee, J. W.: Primary Streptococcal Peritonitis in a Child with Septicemia Ending in Recovery, *Brit. J. Dis. Child.* **10**:258, 1913.

12. Behrendt, R. A.: Experimental Peritonitis Produced by Injection of Bacteria, *Proc. Soc. Exper. Biol. & Med.* **31**:543 (Feb.) 1934.

13. Wegner, G.: *Arch. f. klin. Chir.* **20**:51, 1876.

14. Pawlowsky, A. D.: *Centralbl. f. Chir.* **14**:881, 1887.

15. Steinberg, G., and Ecker, E. E.: *J. Exper. Med.* **46**:362, 1928.

for the intestine and peritoneum. Steinberg and Goldblatt,<sup>16</sup> using virulent *Bacillus coli*, found that intraperitoneal injection of saline suspensions produced bacteremia in dogs, but no deaths. Tragacanth suspensions, however, produced severe toxemia and death. Bolton<sup>17</sup> showed that colloidal dyes passed through the wall of the peritoneum and capillaries into the blood more slowly than crystalloids. Starling demonstrated a relationship between the osmotic pressure of blood proteins and the absorption of fluid by the blood vessels. By increasing the protein content of a peritoneal saline solution the absorbing power was reduced to the intracapillary hydrostatic pressure, and no further absorption occurred. He stated that in the saline suspensions the organisms rapidly pass into the blood stream and are destroyed before any great amount of toxin has been produced. David and Sparks<sup>18</sup> noted the protective action of a plastic peritoneal exudate in preventing the passage of diphtheria toxin from the dog's peritoneum into the blood stream.

Dandy and Rowntree<sup>19</sup> expressed the belief that absorption from the peritoneal cavity is usually hemic rather than lymphatic and did not support the view of the intraperitoneal flow to the diaphragm. This is of interest in connection with the metastatic pleural, pulmonary and pericardial lesions. Woolsey, however, took the opposite view and was supported by the work of Buxton and Torrey,<sup>20</sup> who injected lamp black and typhoid bacilli intraperitoneally and found the maximum concentrations in the liver and spleen.

Wallgren, using intraperitoneal inoculations in rabbits, found that he could produce fatal peritonitis only in susceptible animals. This method does not, of course, simulate pharyngogenic hematogenous streptococcic peritonitis in man.

#### PATHOGENESIS

The clinical features of the disease generally known as primary streptococcic peritonitis point to the throat as the primary source of infection in most cases in which a careful history is obtainable. We have reproduced the disease in rabbits by means of intravenous injection of strains recovered from patients with the disease. Antigenic studies

16. Steinberg, S., and Goldblatt, H.: Studies on Peritonitis, *Arch. Int. Med.* **39**:446 (March) 1927.

17. Bolton, C.: Absorption from the Peritoneal Cavity, *J. Path. & Bact.* **24**:409, 1921.

18. David, V. C., and Sparks, J. L.: The Peritoneum as Related to Peritonitis, *Tr. Am. S. A.* **46**:362, 1928.

19. Dandy, W. E., and Rowntree, L. G.: Peritoneal and Pleural Absorption with Reference to Postural Treatment, *Ann. Surg.* **59**:587, 1914.

20. Buxton, B. H., and Torrey, S. C.: Absorption from the Peritoneal Cavity, *J. M. Research* **10**:3, 1906.

established the similarity of strains. The pathologic lesions in both the human patients and the animal subjects were almost identical. Our bacteriologic and histopathologic studies have established the true hematogenous, metastatic, septicemic nature of the disease arising from a primary focus in the pharynx. The mechanism of peritoneal involvement may be directly through the blood stream, but we are of the opinion that it occurs through the focal hemorrhagic and ulcerative lesions in the intestine. The organisms are brought to the intestines in the blood stream and are excreted through the intestinal wall into the lumen of the intestine. We repeatedly recovered the organism in the feces after intravenous inoculation, as we had previously reported, with the bacilli of Sonne-Duval and Flexner dysentery. The intestinal lesions are produced by the streptococcic toxin. The organisms in the intestine, viable and potent, then pass out through the focal lesions into the peritoneal cavity. The absence of intestinal necrosis in some cases does not invalidate this view as the effects of toxin on the intestinal mucosa must not necessarily produce visible lesions in order to render the wall permeable. There is ample experimental evidence to support this contention. The production of visible intestinal lesions depends on the strength of the toxin, the virulence of the bacteria and the length of time during which they act; finally, many of our peritoneal cultures, both of our patients and of the rabbits, were contaminated with *Bacillus coli*, strongly suggestive of the intestinal origin of the streptococcus. The absence of the organism from the rabbit's intestine as shown by control studies before each animal was used and the presence of the organism in the feces after intravenous injection, accompanied by necrotic lesions in the intestinal wall and peritonitis in which both the *Streptococcus* and *Bacillus coli* were found, constitute fairly conclusive evidence of the mechanism involved in the production of pharyngogenic hematogenous streptococcic peritonitis.

NOTE.—Since this paper was submitted for publication two additional cases have been studied. The first was that of a man aged 26 who was admitted to the hospital on April 27, 1935. Death occurred fourteen days after the angina and seven days after the onset of acute abdominal symptoms. The second was that of a man aged 46, who was admitted to the hospital on May 5, 1935. Death occurred eight days after the angina and one day after the onset of acute abdominal symptoms. Str. alpha (viridans) was recovered in both cases. Post-mortem examination was made. The results of the clinical, bacteriologic and pathologic examinations and the studies on animals duplicated those reported in the paper in their essential details.

# CARCINOMA OF THE CERVIX UTERI

## CLINICAL STUDY OF NINE HUNDRED AND FORTY CASES

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The aspects of cancer which have received most attention in the literature of recent years have been its etiology, its early diagnosis and its treatment. This is no doubt as it should be, and yet much can be learned from the analytic survey of large numbers of cases from the standpoint of the clinical symptoms presented by the patients, the age incidence and the associated physical findings. For example, the duration of bleeding before medical advice is sought should throw an interesting light on the patient's alertness or apathy to this ominous symptom and serve as a justification of the efforts being made to educate women on this point. Again, the question arises whether cancer always can be checked in an early stage even when the patient does pay prompt heed to the symptoms or whether, on the other hand, the patient may not be doomed in many cases no matter how intelligent and alert she may be.

The study of 940 cases of cervical cancer from the gynecological department of the Johns Hopkins Hospital has been undertaken from this general standpoint without any great effort to divide the patients into groups. The results, as will be seen, support my impressions on certain points, while in other respects they are somewhat unorthodox. It was scarcely to be expected that the study would reveal any outstanding sign or symptom which would materially aid in diagnosis: though medical science has advanced with great strides during the past forty years, the knowledge of cancer seemingly well illustrates Bacon's rather unkind comment on medicine in general: "Medicine is a science which has been as we have said, more professed than laboured, and yet more laboured than advanced. The labour having been in my judgement rather in a circle than in progression. For I find much iteration and small progression."

### HISTORICAL BACKGROUND

Before presenting the results of this investigation it seems worth while to sketch briefly the development of the clinical knowledge of cervical cancer, if for no other reason than that my own experience has shown me how difficult it is to get the historical data in any collected form without laborious search through many often rather inaccessible sources.



Ancient authors rarely mentioned this lesion as such, though innumerable papers are devoted to lesions of the breast and skin. The Ebers Papyrus advised that a "woman with a devouring disease of the vulva should be treated with an ointment of arsenic and vinegar," a therapeutic palliative that still is employed in one form or another. Centuries before, in India, Ramayana was advising that cancerous growths be removed with red hot irons. Celsus (30 B. C.-38 A. D.) appreciated the lumpy quality of cancer as a diagnostic aid, especially the condition of the axillary lymph glands in cancer of the breast. And one of his aphorisms has held through the centuries, viz. "only the beginning of cancer admits cure." Albus expressed the same idea in his voluminous treatise on tumors, in which he noted: "When cancer has become old and large you should have nothing to do with it. I have never been able to cure it, nor have I ever seen any one who has." Charlatans flourished in those days as they do now; at this same time Pliny the Younger was advising that "carcinomatous sores are treated with hare's rennet sprinkled upon them with an equal proportion of capers in wine." However, Pliny's remedy is more rational than those employed by the many quacks of the present day. Galen (131-203 A. D.) added his pneumodynamic theory to the doctrine of a pathologic condition of the humors upheld by Hippocrates, pointing out that women of melancholic disposition were especially subject to cancer, particularly after the menopause. He added that when menstruation is regular woman is exempt from the disease. He recognized its malignancy and advocated a combined therapy of medical and surgical measures and stressed the necessity of early diagnosis. Aetius of Amida (502-573 A. D.) in the collected works of Rufus of Ephesus offered the first clear description of cervical cancer. "The tumor was usually at the cervix, hard, resistant, and even to the touch, and reddish, almost livid. From it came a thin watery reddish-yellow discharge." Paulus of Aegina (625-690 A. D.) claimed that it was possible to differentiate between chronic metritis and cancer of the uterus with the aid of a vaginal speculum devised by Archigenes. The value of this instrument was not appreciated, and its use was soon limited and later given up. In the eleventh century, Avenzoar (1070-1162) introduced the nutrient enema, and in the same century Petroncellus advocated digital exploration in the examination for cancer of the rectum and uterus.

In the sixteenth century, Daniel Sennert (1572-1637) of Prague severely criticized the views then existing about the nature and classification of cancer, and he advanced the theory of the contagiousness of cancer. He compared cancer to leprosy and elephantiasis and from this deduced its transmissibility. To support Sennert, Zacutus Lusitanus, a Jewish physician in Portugal, presented the following case: "A poor woman who had suffered many years from an ulcerated cancer of the

breast, slept at night on the same couch with her three sons, and all three became afflicted." The contagiousness of cancer is accepted by many even today, and this belief is not limited to the laity. In 1777, a Mr. Nooth inoculated himself with tissue and fluid from a cancerous growth, but the experiment failed. Copland cited an instance in which the husband developed cancer of the penis following coitus with his wife who was suffering from cervical carcinoma. In 1865, Moore suggested that cancer was a local disease and that changes elsewhere in the body or possible serologic variations were not the result of growths. He asserted, moreover, that the recurrence of cancer following operative removal is due to the fact that some of the growth has been left and that some persons are more susceptible to cancer than others. Shortly after this, Waldeyer, Cohnheim and others inaugurated the modern trend of thought, which it is scarcely necessary to review in this paper.

#### SYMPTOMS

Symptoms presented by the patients are listed in order of their frequency.

Complaint	Cases	Incidence, Percentage
Metrorrhagia .....	243	25.8
Pain in the lower quadrant of the abdomen.....	112	11.9
Irregular menstrual periods with spotting.....	72	7.6
Irregular, prolonged menstrual periods.....	66	7.0
Tumor; vaginal mass.....	49	5.2
Bleeding after coitus.....	45	4.8
Bleeding with foul discharge.....	38	4.0
Foul bloody discharge .....	37	3.9
Odorless discharge .....	35	3.7
Irregular periods with foul discharge.....	25	2.6
Irregular periods with bloody discharge.....	24	2.5
Odorless bloody discharge.....	24	2.5
Irregular periods with odorless discharge.....	21	2.2
Weakness with bleeding.....	21	2.2
Urinary symptoms with bleeding.....	20	2.1
Urinary symptoms; no bleeding.....	14	1.5
Lower quadrant pain and backache.....	14	1.5
Irritating odorless discharge.....	11	1.2
Foul discharge .....	10	1.0
Piles; rupture; change of life.....	9	0.9
Dysmenorrhea .....	8	0.9
Back pains .....	7	0.7
Arthritis; joint pains.....	6	0.6
Tumors with discharge.....	4	0.4
Chills; fever .....	3	0.3
Urinary symptoms with bleeding and discharge.....	3	0.3
Headaches .....	3	0.3

*Bleeding.*—Vaginal bleeding in one form or another leads the duality of cardinal symptoms, bleeding and discharge, occurring in 620 cases (65 per cent). Metrorrhagia was present in 243 cases (25.8 per cent), without noticeable leukorrheal discharge being present. However, every gynecologist knows that many patients deny the presence of a discharge or "whites" and that in not a few of them moderate or even profuse vaginal discharge is found on examination. Thus the value of designating this group of cases as characterized by bleeding alone is questionable.

Few women who come to the public clinics keep careful records of their menstrual cycle, so that the 138 cases (14.6 per cent) represent only those in which I felt certain there was a definite upset in menstrual rhythm. Increased frequency of the menstrual period is the most common change, but a few women stated they experienced periods of amenorrhea; in one instance it was of eight months' duration in a patient 33 years of age. The age of the patients rules out most possible menopausal changes, as all of them were under the age of 40.

*Postcoital Bleeding.*—Spotting after intercourse occurred in only 45 patients (4.8 per cent). This is a surprisingly small percentage. In many of the early cases there is sufficient change in the surface epithelium to explain the occurrence of bleeding following trauma. The basal layer loses its normal protective strength, and thus the capillaries are exposed; the delicate network of papillary outgrowths readily break, and the slightest touch will result in a venous ooze.

*Duration of Bleeding.*—The average length of time that bleeding persists is approximately six months. The maximum period of bleeding with scant leukorrheal discharge was thirteen years. When this patient was examined, she was found to have an operable growth. The condition of another patient, a 26 year old colored multipara, was diagnosed as being marked cervical infection. Cauterization was advised, but the patient refused to have it done. One year later she returned to the clinic, and carcinoma with parametrial invasion was found on examination. Spotting after intercourse was present in another patient following a subtotal hysterectomy two years before; she complained of dyspareunia. At the time of operation the cervix had been treated conservatively, but no microscopic study had been made.

The severity of the hemorrhage does not, in all cases, indicate the extent of the disease, nor does the length of time the patient has had the condition necessarily suggest that the case is hopeless. Patients with profuse intermenstrual bleeding and profuse periods have been operated on successfully, while the condition of many without any apparent bleeding has been diagnosed as "hopeless."

*Vaginal Discharge.*—Usually associated to some extent with bleeding, vaginal discharge was present in 20.6 per cent of the cases. Half of the patients denied the presence of a noticeable odor. No bacterial studies on these patients were made, but the studies made by Philipp<sup>1</sup> support my belief that control of the bacterial infections will not only

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1. (a) Philipp, E.: Zur Virulenzfrage der Streptokokken, *Klin. Wchnschr.* 2:1925 (Oct. 15) 1923; (b) Virulenz Bestimmung von Blutkeimen, *München. med. Wchnschr.* 70:493 (April 20) 1923; (c) Statistik der Karzinome des Collum uteri und der vagina aus den Jahren 1923-1925, mit kritischen Bemerkungen zur Therapie, *Strahlentherapie* 43:102, 1932.

alter the type of discharge but in most instances alleviate much of the pain. The value of bacteriologic studies of the cervix in this condition is doubtful because of the varied flora always present in the vagina.

*Pain.*—Limited to the lower abdominal quadrants, pain was present in 112 cases (11.9 per cent). In half of these the pelvic examination suggested a secondary adnexal inflammatory process. Backache associated with lower abdominal pain was present in 14 cases (1.5 per cent). In no case with the growth localized in the cervix and with no involvement of the adnexa and broad ligaments was pain present. The pains are so varied in type that it is not possible to use them as a diagnostic aid. The cervix is peculiarly insensitive to pain, and the pain is not experienced until the process has invaded the parametrium. Invasion of the rectum and the bladder produces symptoms characteristic of the site, while lateral invasion may exert pressure on the nerve trunks, with resultant symptoms in the lower extremities.

Though the presence of pain in most instances does signify invasion of an ineradicable tumor, there are many patients with secondary infections who often present pains of a more severe type than would be expected from the stage of the disease. Pain should not limit the examination, nor should it necessarily serve as a guide for treatment.

*Urinary Symptoms.*—Four hundred and seventy-three (50.3 per cent) of the patients gave a history of irritation of the urinary tract, and the records on the majority of the patients are thorough enough to rule out previous infections of this tract. Fourteen (1.5 per cent) patients visited the clinic because of urinary complaints alone, while 3 (3 per cent) had symptoms suggesting pyelitis and had been treated before admission because of renal infection. The following table lists the urinary symptoms in the order of their incidence:

Complaint	Cases	Incidence, Percentage
Nocturia (3 or more times) . . . . .	192	20.0
Nocturia; frequency . . . . .	70	7.4
Nocturia; dysuria . . . . .	49	5.2
Dysuria . . . . .	45	4.8
Dribbling; incontinence . . . . .	41	4.3
Burning . . . . .	25	3.0
Burning; nocturia . . . . .	26	2.7
Burning; frequency . . . . .	21	2.2
Burning; frequency; nocturia . . . . .	18	1.9
Dysuria; nocturia, frequency . . . . .	18	1.9
Frequency . . . . .	13	1.4
Hematuria; nocturia . . . . .	13	1.4
Dysuria; burning; frequency; nocturia . . . . .	13	1.4
Frequency; dysuria . . . . .	10	1.0
Urgency . . . . .	7	0.7
Hematuria . . . . .	4	0.4

It is known that any one, or all, of these symptoms may arise from irritation of any portion of the urinary tract and that their presence calls for an effort to locate their origin.

The following case is significant.

A white woman, aged 23, was recently admitted to the medical service with the diagnosis of uremia; she had been vomiting for two weeks and gave a history of spotting following coitus for two years. Although she had been under medical supervision by her private physician over this period and had made known her vaginal bleeding to him on numerous occasions, no pelvic examination was ever made. She had had three normal pregnancies, with a history of edema of the extremities following the last. Pelvic examination revealed a large necrotic cauliflower-like mass filling the vaginal vault, with extensive involvement of the broad ligaments. An endeavor was made to catheterize the kidneys to relieve the renal suppression, but marked obstruction of the ureteral lumen made this impossible. The course was rapidly downward, and the patient died a typical "uremic death" several days after admission.

Faerber<sup>2</sup> found that in 88 (58.7 per cent) of 150 patients dying of carcinoma of the cervix there was definite evidence of disease of the bladder. He listed the incidence of urinary lesions found as follows: simple cystitis, 11; cystitis hemorrhagica and exulcerans, 13; cystitis gangraenosa, 26; tumor metastases, 8; direct invasion of the tumor, 9; and suppurating cavities, 10. In 84 cases (56 per cent) there was definite ureteral involvement and in 108 cases (72 per cent) the kidneys showed damage. It is also very interesting to note that there was bilateral hydronephrosis in 55 cases and unilateral hydronephrosis in 40; pyonephrosis in 20 and pyelitis and pyelonephritis in 19. Warren<sup>3</sup> in his series noted that renal involvement was the cause of death of one third of his patients. Williams found definite hydronephrosis in over 85 per cent of his 78 postmortem studies on patients with cervical carcinoma and demonstrated renal damage in every case. Kraul<sup>4</sup> in Peham's clinic found pyelitis or pyelonephritis in 85 per cent of the cases and uremia as the cause of death in 50 per cent. His postmortem studies revealed that the damage to the kidneys resulting from hydronephrosis was secondary to ureteral obstruction.

The postmortem studies in this series are few, because most of the patients with a so-called hopeless condition are either transferred to the city hospitals or sent home; however, postmortem studies on 24 patients showed definite involvement of the urinary tract in 65 per cent. According to Band and Wade,<sup>5</sup> death from cervical cancer is usually due to the three following complications: (1) renal infection, either from an ascending or from a blood-borne pyelonephritis; (2) renal suppression,

2. Faerber, H.: Woran sterben die nicht operierten bzw. Rezidiv gewordenen Uterus Karzinomkranken? *Ztschr. f. Geburtsh. u. Gynäk.* **99**:213, 1931.

3. Warren, Shields: The Grading of Carcinoma of the Cervix as Checked at Autopsy, *Arch. Path.* **12**:783 (Nov.) 1931.

4. Kraul, L.: *Zentralbl. f. Gynäk.* **47**:1573, 1923.

5. Band, D., and Wade, H.: Vesical Exclusion in Treatment of Carcinoma of Cervix Uteri, *Tr. Edinburgh Obst. Soc.*, 1930, p. 89.

usually from ureteral obstruction, and (3) toxemia from septic absorption. The same authors recognized six definite stages of involvement of the bladder from anterior extension of the tumor: (1) elevation of the bladder floor; (2) fixation of the bladder floor; (3) circulatory changes, as recognized by congestion or petechial hemorrhages; (4) formation of a transverse ridge; (5 and 6) malignant invasion, displaying its presence in the form of an ulceration, of hypertrophic nodules or of a vesicovaginal fistula.

The presence of an extrinsic tumor mass pushing against the bladder is easily overlooked in the early stages, unless there is some change in the outline of the normal vesical floor with visible congestion. It is very likely that early irritation of the base of the bladder results in a variety of urinary symptoms, even when there are no findings from cystoscopic examination. The edema resulting from a compromised lymphatic circulation in most cases precedes the tumor mass and presents two definite stages. The lymphatics in the wall of the bladder are the first to be involved, the walls becoming edematous and presenting a glazed appearance. The second stage follows closely and is characterized by an irregular edema of the mucosa, the so-called bullous edema. It is during the latter stage that the tumor mass may be visible, especially in those areas less affected by the edema. The fixation of the bladder in the absence of infection denotes definite involvement of the wall and often produces a transverse ridge. Finally the wall of the bladder is penetrated, gross hematuria results, and the formation of a fistula occurs in time. Microscopic hematuria may result from vesical congestion secondary to lymphatic stasis.

Ureteral involvement does not necessarily keep pace with the vesical changes, and it is possible to have one without the other, though not for long. Periureteral infiltration by the carcinoma, with its concomitant inflammatory reaction, occurs without recognizable changes in the bladder and produces, in order, hydro-ureter, hydronephrosis and uremia, as the occlusion of the ureters advances. The proximity of the cervix to the ureterovesical area makes it practically impossible for the malignant process to reach any advanced stage without involving the ureters; however, it is well known that the ureteral wall is peculiarly resistant to the invasion of cancer and that the occlusion is the result of pressure. If the tumor extends into the parametrium, treatment by irradiation occasionally results in ureteral damage, though the number of such instances are surprisingly few. With the appearance of the ureteral symptoms, the value of irradiation is diminished, as the destructive action of radium may include the renal tract. Many patients seemingly cured by irradiation and enjoying good health for years suddenly succumb to damage of the renal tract. Some physicians even advocate the

implantation of ureters in those patients suspected of having suffered ureteral damage. However, I feel that so radical a procedure as ureteral transplantation should never be resorted to except under most unusual conditions. In most instances ureteral drainage can be secured by proper measures applied before and after the therapy for carcinoma.

The appearance of urinary symptoms in patients known to have cervical carcinoma is sufficient indication for a thorough examination of the urinary tract before exposing the patient to either surgical or radiologic procedure. The presence of hematuria in such patients commands at least a study of the bladder, while a vesicovaginal fistula in an untreated patient is usually indicative of a far advanced stage, but many steps can be instituted to make such a patient comfortable. Comfort for the patient presupposes a knowledge of the degree of involvement of the urinary tract. Sufficient drainage will make the final days of the patient with a so-called hopeless case less painful and easier to control with sedatives. In reviewing these urologic conditions in this series it was depressing indeed to note the number of patients who had received oral medication for their symptoms, without any form of physical examination, before coming to the clinic.

*Constipation.*—This condition occurred in various degrees of obstinacy in many of the patients and often was associated with hemorrhoids, but in the entire series only 5 histories suggested rectal involvement before the formation of a fistula. The first rectal symptom is often a proctitis, usually associated with a foul vaginal discharge and is invariably relieved when the type of discharge changes. The patients in this series were not sufficiently explicit on this point, and thus the conclusions are based on very few cases. Following the congestion of the rectal mucosa a varying degree of rigidity appears, slowly forming in some cases a scarlike retraction and narrowing of the lumen. Constipation becomes more pronounced and is followed by tenesmus. The rectal mucosa becomes edematous and on examination presents a smooth glassy appearance. The vaginal discharge finally may assume a fecal odor as the last stage with ulceration, and penetration of the rectal mucosa occurs.

*Loss of Weight.*—Loss of weight, as listed by the numerous observers of patients in the gynecological department over a period of forty years, receives varying degrees of accent. Fifteen per cent of the histories make no mention of weight, and one may presume that the patient had not lost sufficient weight to attract her attention. Thirty-three per cent gave either no known loss of weight or a possible slight gain in weight; thus 52 per cent of the series showed definite change in weight. In the histories "some loss" is considered as being from 5 to 10 pounds (from 2.3 to 4.5 Kg.); "moderate to marked," from 20

to 30 pounds (from 9.1 to 13.6 Kg.). The average loss of weight for the 52 per cent of the patients is approximately 15 pounds (6.8 Kg.), with a loss of 65 pounds (29.5 Kg.) over a period of six months as the maximum. Twelve patients sought medical aid primarily because of the loss of weight.

Recently a 33 year old colored nullipara, complaining of loss of weight, increasing weakness and scant spotting following coitus and douches, sought assistance in the clinic because her "clothes no longer fitted her." She had lost 44 pounds (20 Kg.) over a period of six months but was able to continue as a cook in a large club. Examination revealed a large, firm, smooth mass totally obliterating the landmarks of the cervix and extending into the parametrium. There was no tenderness, but the Schiller test was decidedly positive and a biopsy confirmed the results of the test. Following irradiation she had a foul discharge, with cramplike pains in the lower quadrants of the abdomen and frequency of and burning on urination. Opiates were necessary to alleviate the pain. The patient had been examined elsewhere several times during the previous two years because of postcoital spotting, and each time palliation was advised.

The loss of weight does not vary proportionally with the hemoglobin content or the degree of malignant invasion. Although it is commonly present in late stages of the disease, its presence does not serve as a diagnostic aid. However, loss of weight in a woman warrants not only the usual tests and examinations to rule out the possibility of cardio-respiratory lesions but a pelvic examination to rule out the possibility of cancer.

*Anemia.*—The lowest hemoglobin content in our series was 12 per cent, this being in a 36 year old colored multipara who had "moderate" vaginal bleeding for three months, accompanied with foul discharge. On examination the growth seemed localized, and a successful total hysterectomy was performed. Following several transfusions she was discharged from the service with a hemoglobin content of 48 per cent. Four years later she had a hemoglobin content of 95 per cent with no suggestion of recurrence. Another patient had been bleeding for approximately the same length of time; on examination her hemoglobin content was 87 per cent. A subtotal hysterectomy had been done four years before, and she was treated with radium, without success. A woman complaining of loss of weight (25 pounds, 11.3 Kg.) and vaginal bleeding with foul discharge had a hemoglobin content of 95 per cent. The growth, however, had already invaded the parametrium.

The average hemoglobin count of this series of patients was 72 per cent, with the minimum 12 per cent and the maximum 105 per cent. This average is equal to that of a group of young women taken at random and higher than that of a group of an equal number of nurses



working in an institution. Although the estimation of the hemoglobin content does not serve as a diagnostic factor, it is an aid in the medical treatment of the patients with inoperable cancer.

#### RÔLE OF PREGNANCY

The predisposing rôle of pregnancy and labor in the causation of cancer is generally accepted. However, no convincing evidence has been offered to prove that pregnancy possesses either a retarding or a stimulating effect on a malignant growth. Since over 90 per cent of all cases of cervical cancer are said to occur in women with a history of parturition, the appearance of the tumor during the puerperium should not be surprising; indeed, in view of the frequency of cervical carcinoma, it is surprising that its appearance at this time is not more common.

One hundred and three patients (10.9 per cent) of the present series stated that they had never been pregnant; the veracity of the patient is rarely questioned, though it is not a rarity to have a patient admit falsification at a later date. In 13 per cent of the series there was a history of only 1 pregnancy. These figures agree with those of most observers, though Frankl found 3 per cent nulliparas in his series; Johnson and Tyrone<sup>6</sup> reported 3.4 per cent in 926 patients. Frigyesi,<sup>7</sup> in his series of 690 patients, reported 74 per cent multiparous, 12 per cent nulliparous and 14 per cent primiparous. Other observers reporting nulliparas in their series include Martzloff with 5.4 per cent, Kauffmann with 10.1 per cent, Graves with 9.2 per cent and Bartlett and Smith<sup>8</sup> with 10.7 per cent. Mattmüller found 9.7 per cent of the patients to be nulliparas and felt justified in reporting 10 in his series of 440 patients as virgins.

With 10 per cent as an acceptable average figure I call attention to Hinselmann's study<sup>9</sup> of the Prussian statistics in which he found that 10 per cent of the female population over the age of 35 were unmarried. The nuptial knot does not purport pregnancy, nor does celibacy connote virginity, but in a large series the nonconformists of one group probably offset those of the other. Thus statistically speaking, one might say that cervical carcinoma is not influenced by pregnancy.

In the 837 women (89.1 per cent) of the present group with histories of pregnancy, there was an average of 5.16 pregnancies per patient or

6. Johnson, C. G., and Tyrone, C. H.: *Uterine Cancer: Report Covering Period June 1927 to June 1932, Surg., Gynec. & Obst.* **58**:113 (Jan.) 1934.

7. Frigyesi, J.: *Oruoskepzes* **20**:178, 1930.

8. Bartlett, M. K., and Smith, G. S.: *Carcinoma of the Cervix: Study of Cases Treated at the Free Hospital for Women Between 1875 and 1929, Surg., Gynec. & Obst.* **52**:249 (Feb.) 1931.

9. Hinselmann, H.: *Ueber die Prophylaxe des Portiokarzinoms nach Bossi-Spirito, Zentralbl. f. Gynäk.* **55**:3362, 1931.

a total of 4,319. The average for the entire series is 4.6 pregnancies. In England, Lever found that the patients had an average of 5.75 children in his series of 103 cases; this figure is above the average for England, but we cannot assume that frequent parturition causes cancer. In this series I have included known abortions, miscarriages, surgical interventions and spontaneous deliveries. It is of interest that I found three white women with 21 children apiece, while the maximum for the colored group was 14 children.

Stöckl,<sup>10</sup> reviewing 18,000 deliveries in Posen, found only 8 cases of cervical carcinoma (0.04 per cent). There was no evidence in his series to suggest that the growth of cancer is influenced in any way by pregnancy. Experiments by von Graf and Maude Sly on animals suggest that pregnancy does not hasten the growth. However, various observers hold there is an accelerating influence and offer several theories to account for this influence, i. e., hyperemia of the pelvic tissue, disappearance of certain hypothetic protective substances from the blood stream and various changes in the blood, such as an increase in the hypophyseal hormone, as suggested by Hofbauer and others.

Mayer found 18 patients with cancer (1.6 per cent) in a series of 1,106 pregnant women; O'Malley and Walsh stated that it occurs once in each 2,000 deliveries. From the reports in the literature one may conclude that the percentages range from 0.04 per cent to 1.8 per cent with the average below 1 per cent. The rarity of its occurrence does not justify its being disregarded, and cancer must always be considered a possibility in the gravida. Too frequently is bleeding during the puerperium hastily passed by on the assumption that it is an insignificant accompaniment of pregnancy. Profuse bleeding in the pregnant woman is often diagnosed as placenta praevia. It is more difficult to determine the presence of early carcinoma in a pregnant woman than in a non-pregnant woman, but a careful examination of the exposed cervix is indicated in every instance of bleeding. According to Phillip, pregnancy does not affect the treatment, and the early finding of the growth may make it possible to deliver a living child and to cure the mother.

Keller<sup>11</sup> reported the case of a 38 year old multipara with a history of bleeding for three weeks, ante partum; no vaginal examination was made. She was delivered spontaneously at home and three weeks later sought advice for a persistent vaginal hemorrhage. An advanced carcinoma was found. One of the patients in the present series was a 28 year old multipara, with no abnormal prenatal symptoms, who was delivered spontaneously at home. One month later a scant spotting after coitus

10. Stöckl, E.: Kollumkarzinom und Schwangerschaft, *Ztschr. f. Geburtsh. u. Gynäk.* **101**:437, 1932.

11. Keller, R.: Au sujet du dépistage du cancer du col pendant la grossesse. *Bull. Soc. d'obst. et de gynec.* **21**:77 (Jan.) 1932.

appeared, followed shortly by a malodorous discharge. Six weeks after parturition on examination a carcinoma was found. A successful total hysterectomy was performed, and she was free from recurrence ten years later. Another patient, a 37 year old multipara, was delivered spontaneously; her antepartum history is unreliable. Two months after delivery she noticed a scant postcoital spotting. Three months later a thin, foul discharge appeared, and she sought relief. Cancer was found and a total hysterectomy was performed, followed by irradiation. The patient died three months after the operation. The duration of the symptoms and the lapse of time before most patients seek medical attention vary greatly. Proper antepartum and postpartum examination of these women would have permitted an early diagnosis.

Accepting chronic infection as a paramount factor in the etiology of cervical cancer, parturition is the most important cause of these "irritation areas." According to most observers, malignant conditions rarely develop in or near the site of injury but occur on the margin of the subsequent erosions and eversions. The studies of Hinselmann,<sup>9</sup> Bonney, Hunner and Bartlett and Smith<sup>8</sup> have demonstrated well the paucity of malignant conditions in cervixes treated conservatively, and Pemberton in a recent study of 5,962 cervixes which had been either cauterized or repaired reported only 5 carcinomas. Thus the eradication of the unhealthy cervical tissue and the repair of the lacerations resulting from delivery will remove the primordium of cervical cancer.

#### AGE AND RACE INCIDENCE

In the minds of most of the women who come to a public clinic, the age of the menopause is viewed with dread, for it is with this normal physiologic epoch that cancer has been associated since the days of Galen. Many an otherwise normal person is started on the road of chronic neuroticism because of this unfounded fear, enhanced by hearsay and information gleaned from the notices of patent medicines. Carcinoma is no respecter of age, and in this regard the results of the present series agree with those of most observers. In the following table the incidence of corporeal cancer in a large group of patients is noted for comparison:

Age Groups	Patients with Cervical Cancer		Patients with Corporeal Cancer	
		Percentage		Percentage
20-24.....	18	1.9	..	....
25-29.....	60	6.4	4	2.4
30-34.....	88	9.4	1	0.6
35-39.....	146	15.5	11	6.5
40-44.....	162	17.2	18	11.1
45-49.....	149	15.8	28	17.2
50-54.....	124	13.2	48	29.6
55-59.....	80	8.5	28	17.2
60-64.....	57	6.2	14	8.6
65-69.....	30	3.2	5	3.1
70.....	26	2.7	5	3.1
	940		162	

There is 1 case of corporeal cancer to 5.8 cases of cancer of the cervix. Sixty-six and three tenths per cent of the cervical growths in the patients of the present series occurred before the age of 50 years, while 61.7 per cent of the corporeal growths appeared after this period. The average age for the patients with cervical cancer is 46.1 years; for the patients with corporeal cancer it is 52.8 years. Seventeen and seven tenths per cent of the cervical lesions occur in patients before the age of 35, with 8.3 per cent appearing before the thirtieth year.

There is a gradually increasing literature on cervical cancer in extreme youth. Bumm<sup>12</sup> reported an adenocarcinoma in a 7 month old child; this was confirmed histologically by Aschheim, and Scheffey and Crawford<sup>13</sup> reported the same lesion in a child at the age of 22 months.

On the other hand, it is of interest that Donald and Shaw<sup>14</sup> in their series of 177 patients with cancer of the body reported only 1 under the age of 40 years. In the present series there are 16 patients under the age of 40, with 4 under the age of 30 years. Kehrer and Neumann<sup>15</sup> reported the lesion in a 15 month old child, and Taussig<sup>16</sup> presented the case of a 10 year old girl with carcinoma of the body.

The authenticity of many of these cases in extreme youth is doubtful, for the proximity of the wolffian duct opens a possible site of origin for "mixed tumors" of congenital type. Before such cases can be regarded as authentic a thorough histologic examination by more than one accepted authority should be required. In this series, the youngest patient was 20 years old and the oldest was 79.

Without doubt age is a salient factor in cancer of the uterus, but the age incidence must be made to include the early twenties. The appearance of either bleeding or vaginal discharge, regardless of the age of the patient, indicates that an examination of the cervix is advisable.

Over a period of forty years the patients whose cases have been recorded in the gynecological clinic are about evenly divided between the white and the colored races. In this series of 940 patients, 470 (50 per cent) belong to the colored race; thus there seems to be no racial

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12. Bumm, E.: *Karzinomatöses Uterus eines sieben Monate alten Kindes*, Deutsche med. Wchnschr. **35**:1331, 1909.

13. Scheffey, L. C., and Crawford, B. L.: *Adenocarcinoma of the Cervix in a 22 Months Old Child*, Am. J. Obst. & Gynec. **24**:118 (July) 1932.

14. Donald, A., and Shaw, W. F.: *Age Incidence of Carcinoma of the Body of the Uterus*, Proc. Roy. Soc. Med. **22**:19 (Jan.) 1929.

15. Kehrer, E., and Neumann, H. O.: *Uteruskarzinomexstirpation bei einem 1¼ jährigen Kind*, Monatsschr. f. Geburtsh. u. Gynäk. **81**:68 (Jan.) 1929.

16. Taussig, F. J.: *Questionable Uterine Cancers in Very Young Persons*, S. Clin. North America **5**:1437 (Oct.) 1925.

preference of the malignant condition. Fifty-six per cent of the cases of corporeal cancer occurred in the white race.

#### HEREDITY

The patient with cancer cares little whether he is a victim to an inherited susceptibility, to a malformation of tissues or to cancer itself; to the clinician and to the person without cancer, the factor of heredity is of paramount importance. One hundred and thirty-two (14 per cent) of the patients in the present series stated that one or more of their blood relatives had died of "cancer." To serve as a norm, 500 successive medical histories were studied, and an occurrence of 11.5 per cent were found. The value of these observations is doubtful, for it is evident that an accurate genealogic history is not easily obtained. There is no evidence in this series to suggest that either cancer or the predisposition to cancer is hereditary. The fact that several members in successive generations have died of cancer is certainly not proof that the trait, be it a recessive or a dominant character, is passed on in the germ cell. Hutchinson<sup>17</sup> found that in less than 6 per cent of 50,000 cases of death from cancer was there a history of familial malignant disease. Waaler<sup>18</sup> has recently studied the familial histories of 6,000 patients with cancer and found himself confronted with so many extrinsic factors that satisfactory deductions were difficult. He stated the belief, however, that hereditary susceptibility plays a part, as in his series cancer was more frequent among blood relatives. One must not overlook the possibility that these persons are more frequently exposed to the same "cancer-producing" agent.

The paucity of acceptable data on heredity makes it impossible to evolve any valuable conclusions, for it would be necessary to have dependable statistics on several generations. At the present time there is no adequate evidence for assuming that some persons are predisposed to cancer.

#### CANCER IN THE CERVICAL STUMP

In presenting the cases of cancer occurring in the cervical stump after subtotal hysterectomy, we do not intend to enter into a debate as to the efficacy of total hysterectomy over the subtotal operation. Twenty-two (2.3 per cent) cases in our series occurred in the cervical stump, including 1 case of adenocarcinoma. Johnson and Tyrone<sup>6</sup> found 21 cases in their series of 926 patients; 10 of these had received previous cervical treatment. The lapse of time following the subtotal

17. Hutchinson, Woods: *Preventable Disease*, New York, Houghton Mifflin Company, 1909.

18. Waaler, G. H. M.: *Ueber die Erbllichkeit des Krebs*, Oslo, Jacob Dybwad, 1931.

operation and the appearance of the malignant condition in this series showed fourteen years as the maximum and one year as the minimum, with an average of five years. With six months as the average duration of symptoms in this series, I believe it possible to classify these cases into two groups. If the growth appears after a period of two years it is considered a new growth; with this rule the percentage of carcinoma in the stump is reduced to less than 0.2 per cent. This low percentage can be further reduced if, during the surgical removal of the uterus, the cervix is either cauterized or repaired as indicated.

#### SUMMARY

The importance of early diagnosis has been appreciated for more than 3,000 years and, except for the advent of the microscope, little change has taken place in the present methods of diagnosis.

In this series of 940 cases the average age was 46.1 years, with cancer occurring in 66.3 per cent before the age of 50 years. The patients were evenly divided between the two races, and over 10 per cent stated that they had never been pregnant.

Bleeding from the vagina, in one form or other, is the most frequent factor in bringing the patient to seek medical aid. The duration of bleeding averages six months. Postcoital spotting occurs in less than 5 per cent.

Involvement of the urinary tract was present in 50 per cent of the cases, with nocturia the most frequent complaint.

Pregnancy apparently does have some influence on the growth of the tumor, and the commonly attending laceration of the cervix is a cardinal factor in producing chronic irritation.

The average hemoglobin content is 72 per cent, which is no lower than that of normal women doing institutional work.

Loss of weight has no diagnostic value, as the average loss was only 15 pounds (6.8 Kg.), and 50 per cent of the patients did not report any change in weight.

The possible influence of heredity is still a disputed question.

Pain is present in such a variety of pelvic lesions that it is of no diagnostic aid; rarely, if ever, does it appear with cervical cancer before parametrial invasion, but it may be seen in even early cases combined with other pelvic lesions.

Twenty-two cases occurred in the cervical stump following subtotal hysterectomy, with an average lapse of five years. The growth may be assumed to have been preexistent if it occurs within two years after the operation. The incidence of cancer of the stump in this series is less than 0.2 per cent.

Rectal invasion is rare except in advanced cases, but it is probably more frequent than is suspected.

Loss of weight, amount of bleeding, type or severity of pain, age, heredity and number or frequency of pregnancies do not govern necessarily either the malignancy or the degree of invasion in carcinoma of the cervix. The complaints are so manifold that the appearance of a patient, regardless of her complaints, warrants a thorough examination, which is not complete without a speculum exposure of the cervix

## A REVIEW OF UROLOGIC SURGERY

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*(Concluded from page 344)*

### URETER

*Occlusion.*—Bugbee<sup>33</sup> reported that he had performed nephrectomy, following irradiation of the uterine cervix for carcinoma, in 6 cases at the Woman's Hospital since 1930. In the past year, 2 other cases were seen; in one there was occlusion of both ureters, and in the other unilateral occlusion; in both instances, the occlusion was secondary to irradiation of the uterus. All except 1 of the patients in Bugbee's series of cases complained of bleeding from the vagina; all but 1 revealed a squamous cell carcinoma of the cervix at biopsy. All except the last were treated at the Woman's Hospital, with radium, one or more tubes being inserted into the cervical canal for a minimal dosage of 1,787.5 mg. hrs. and a maximal dosage of 4,857.68 mg. hrs. In 3 cases, needles were also inserted into the cervix, and 5 patients received treatment with roentgen rays of high voltage. In 4 cases, the carcinoma had extended to the wall of the vagina. None of the patients revealed evidence of metastasis when first treated, or had symptoms which were referable to the urinary tract at the time of the first irradiation. The urine was normal in all but 1 case. The obstruction of the ureter was unilateral in 7 cases and bilateral in 1 case; the average distance of the obstruction from the ureteral orifice was 4 cm., and in 3 cases there was a uretero-

33. Bugbee, H. G.: Ureteral Occlusion Following Radium Implantation into the Cervix, *Tr. Am. A. Genito-Urin. Surgeons* 27:329, 1934.



vaginal fistula distal to this point of obstruction. In the first 6 cases, a functionless kidney, the condition of which was the result of pyonephrosis secondary to ureteral occlusion, was removed. The time which had elapsed between the irradiation and the nephrectomy in these cases was as follows: twenty-two months, seven months, five months, seven months, twenty-two months and nine years, respectively.

Deane described three reactions to radiation, in terms of surface reaction: The first was an irritation, which occurred within twenty-four hours; the second was an erythema, which appeared at the end of a month and was the result of a temporary localized vasomotor paralysis, a condition which may progress to destruction of tissue; the third, which formerly was called a delayed radium burn, was a specific radiation change and was the result of an obliterative endarteritis. The cases of vesical injury that he reported were of the third type and appeared in a minimum of ten months after irradiation.

*Trauma.*—Sisk<sup>34</sup> stated that a large number of operations have been described for the repair of operative injuries of the ureter, but all are based on the principles of end-to-end, end-in-end or side-to-side anastomoses. The technic used by Sisk combines the principles of simplicity, splinting of the ureter, maintenance of caliber and satisfactory drainage. It is the procedure of choice for the repair of ureters thus traumatized, with certain exceptions which will be mentioned later. The technic is as follows: A ureteral catheter, as large as will move freely through the ureter without interfering with the circulation, is introduced into the ureter and passed into the pelvis of the kidney. Introduction may be made through a cystoscope or the catheter may be passed each way from the point of injury, the lower end being brought out through the urethra later. Over this catheter, end-to-end anastomosis is performed, the sutures of fine catgut being passed through the serous and muscular layers of the ureter. With satisfactory drainage, the catheter may be left in place for many days to prevent contraction of the lumen during healing.

Variations of this procedure are necessary in cases in which the injury is sufficiently low to permit reimplantation into the bladder, which is preferable; or when a segment which has been removed is of sufficient length to cause tension. If there is tension, satisfactory healing will not occur and implantation into the intestine is the operation of choice. Cases in which there are old injuries must be considered as separate entities. After appropriate examinations to determine the condition of the kidneys and ureters, a satisfactory procedure must be selected. This may be a plastic repair, implantation into the bladder or intestine, nephrostomy or nephrectomy.

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34. Sisk, I. R.: *Operative Injuries of the Ureter*, Tr. Am. A. Genito-Urin. Surgeons 27:287, 1934.

*Ectopic Outlet.*—Deming<sup>35</sup> reported that ectopic ureters opening into the vagina produce uniform symptoms of vaginal dripping of urine, together with normal urination. The opening of an ectopic ureter into the vagina is on the anterior wall of the vagina, near the midline, and anywhere from the hymen to the uterine cervix. A supernumerary ectopic ureter opening into the vagina always runs to the upper pole of the kidney. The right side is more frequently involved than the left. The kidney attached to the ectopic ureter is of small functional value and is prone to infection. No attempt should be made to conserve such a ureter and kidney. Heminephrectomy may be done if the vessels to each kidney are distinct. Once the kidney is infected, nephrectomy is indicated. Total ureterectomy is a satisfactory method of treatment when infection is not present.

*Empyema.*—Smith<sup>36</sup> reported a case in which the right ureter terminated superiorly in a fibrous insertion in the peritoneum. In this fibrous termination, a few tubules were found. The lower end emptied into the bladder in an anomalous situation; the entire pelvic portion of the ureter was dilated and full of pus. It had produced partial obstruction to the emptying of the bladder by pressure on the trigon from behind, and the infection had caused a toxemia. The entire ureter was removed, and the defect in the right lateral wall of the bladder was closed with a continuous suture of catgut. The neck of the bladder admitted the tip of the finger readily. A tube was left in the bladder, a cigaret wick was inserted in the prevesical space, and a rubber drain was placed in the right iliac fossa, behind the peritoneum.

*Regurgitation.*—Vermooten and Neuswanger<sup>37</sup> said that complete excision or incision of the ureterovesical valve of a dog will always result in incompetence, as shown by regurgitation up the ureter of contents of the bladder. Regurgitation of uninfected or infected urine up a normal ureter will not cause dilatation of the ureter. Ureteral dilatation will be caused by regurgitation up an infected ureter. Ascending infection does not necessarily occur when infected contents of the bladder regurgitate up a normal ureter. Ureteral infection may occur as the result of ulceration of the epithelium of the ureter. This infection may progress by direct extension upward and downward in the loose areolar tissue of the tunica propria of the mucosa, without the aid of the lymphatics. If this infection extends beneath the epithelium of the

35. Deming, C. L.: Ectopic Vaginal Ureter. *Tr. Am. A. Genito-Urin. Surgeons* 27:297, 1934.

36. Smith, G. G.: Empyema of the Ureter Associated with Aplasia of the Kidney. *Tr. Am. A. Genito-Urin. Surgeons* 27:321, 1934.

37. Vermooten, V., and Neuswanger, C. H.: Effects on the Upper Urinary Tract in Dogs of an Incompetent Uretero-Vesical Valve. *J. Urol.* 32:330 (Oct.) 1934.

mucosa which lines the pelvis and calices of the kidney, pyelitis results. The ureteritis in these instances usually is limited entirely to the tunica propria and does not ordinarily extend to the ureteral musculature. Periureteric inflammation was not observed in any of these experiments.

*Anastomosis.*—Zollinger<sup>38</sup> said that previous experimental evidence indicates that better results can be obtained in uretero-intestinal anastomosis if the ureter is temporarily protected from contamination. Open lymphatics of the ureter that become contaminated at the time of operation probably are a major route of ascending infection of the kidney.

A mechanical appliance is described which fulfils the experimental requirements for protection of the ureter and which permits the immediate aseptic drainage of urine. The mechanical efficiency of the drainage button which is described can be improved markedly by changing the design to allow the parts to screw together, thus preventing their separation. It is suggested that a drainage button of the same design as the present one, but much larger, could be used advantageously.

*Ureterostomy.*—Fresnais<sup>39</sup> said that only a few cases in which ureterostomy had been performed had been recorded up to 1920. In 1921, iliac implantation of the ureter was described by Legueu and Papin. Since that time, Papin, Marion and Rosenkranz have employed cutaneous ureterostomy in cases in which exclusion of the bladder was necessary after nephrectomy for tuberculosis, but Thevenot in 1924, and Lepoutre in 1926, still maintained that, owing to the rarity of cases in which this operation had been employed, its value could not yet be estimated.

If important disturbances of the bladder appear after nephrectomy for tuberculosis, examination must first establish the cause of these troubles. If they arise from stones or inflammation of the bladder, the condition may be treated as if the patient did not have tuberculosis. If, on the other hand, the inflammation is of a tuberculous nature, the primary focus of infection must be determined, and the possibility of a vesico-ureteral reflux must be considered.

A cyst in the bladder which reappears indicates a tuberculous kidney, and in such cases the walls of the ureter generally are hardened. If the cyst, however, has persisted even after nephrectomy, the tuberculous infection may come from the ureter of the side which has been subjected to operation, and the remaining kidney may not be involved. The infection also may arise from the bladder itself. The infection in the bladder has proved tenacious in most cases.

38. Zollinger, Robert: Uretero-Intestinal Anastomoses: The Use of Mechanical Anastomosing Apparatus, *Surg., Gynec. & Obst.* 59:796 (Nov.) 1934.

39. Fresnais, Jean: L'urétérostomie cutanée dans le traitement des cystites rebelles chez les néphrectomisées pour tuberculose, *J. d'urrol.* 38:315 (Oct.) 1934.

The reflux to the remaining kidney has been studied only recently by means of roentgenography. The roentgenogram reveals the point at which the ureter enters the bladder, and shows whether the reflux is confined to the ureter or whether it mounts to the renal pelvis; sometimes the ureter is dilated; sometimes it is flexuose or kinked. The bladder may be normal, or it may have shrunk in size. The reflux causes pain and frequent or irregular urination, because of the diminished size of the bladder. The major importance of the reflux lies, however, in its tendency to infect the remaining kidney. The intensity of pain and the existence of reflux are the two factors which determine exclusion of the bladder. By ureterostomy, therefore, the patients may be relieved and the remaining kidney saved from contamination.

Cutaneous ureterostomy has the advantage over intestinal ureterostomy in being less hazardous, although in some cases the latter has given excellent results (Papin, 1925). It is, however, too risky in cases in which a single kidney remains.

The advantage of ureterostomy over cystostomy is evident. The latter does not prevent reflux and hence does not exclude contamination of the kidney, or does it entirely relieve the patient. In several cases on record, cystostomy had to be followed ultimately by ureterostomy.

With nephrostomy, the reflux is entirely prevented and pain is relieved, but this procedure does not completely exclude the bladder unless the ureter is tied or even severed. Nephrostomy injures the renal parenchyma and reacts on the anatomic status of the kidney. It also promotes serious infection by reason of the catheter. The necessity of inserting the catheter in the back is, furthermore, a great inconvenience to the patient. The argument that after nephrostomy the normal course of the urine may be reestablished after a certain time of detoxication does not hold in view of the fact that complete assurance of exclusion of the bladder is given only if the ureter is put out of commission. Nephrostomy is, therefore, in effect as final as ureterostomy.

Ureterostomy is contraindicated if the ureter is too narrow, or if the kidney itself is infected. In the latter case, nephrostomy is always preferable because it allows better drainage of pus pockets than does ureterostomy.

The technic of ureterostomy is now confined to iliac implantation. A sufficiently long portion of the ureter must be isolated to permit easy conduction to the skin. After implantation, a Nélaton catheter is inserted as far as the renal pelvis, in order to prevent retention. The catheter is changed from time to time. After healing, only a short catheter is left in place, and the patient can attend to this. A rubber pocket serves to receive the urine, which in nearly all cases will be discharged drop by drop.

The results of ureterostomy are satisfactory and permanent, all patients having been immediately relieved. The influence of the operation on the ureter can only be called beneficial, no dilatation or loss of tone having been observed. The roentgenogram revealed dilatation of the renal pelvis and calices, but this was most likely the result of the reflux which was present before the operation.

The only objection to ureterostomy lies in the possibility of an ascending infection; this has been observed frequently, but only rarely has it been of an extremely serious nature. As infection after nephrostomy is just as likely, the possibility of infection after ureterostomy seems to offer no decisive argument against its practice.

#### BLADDER

*Tumors.*—Spooner<sup>40</sup> reported that of 163 definite cases of tumor of the bladder in which necropsy was performed, metastases were found in 49 (29 per cent). Of the patients who had metastatic lesions, 65 per cent were considered as amenable to surgical treatment; many had the possibility of surgical cure as far as could be determined clinically. The most frequent site of malignant extension is the regional lymph nodes; they were involved in 34 (69 per cent) of the 49 cases. Lymph nodes represented the only apparent site of metastasis in 12 (24.4 per cent) of the cases. Metastatic growths were found in one or more distant viscera in 24 (48.9 per cent) of the cases. The liver was involved in 14 of these cases and the lung in 9. Skeletal involvement is not an ordinary finding in metastasis of tumor of the bladder. Estimation of the incidence of metastases, based on many surgical studies, may be inaccurate because exploration for metastases was not made. Clinical data presumably indicative of extravesical extension are often obtained by rectal examination, by elicitation of a long history, by determination of a large lesion cystoscopically, by disclosure of a lesion by biopsy, by a malignancy which is graded 3 or 4 and by the presence of persistent pain which is unexplained by the local lesion. Of the 163 cases in this series, 29 per cent presented metastatic lesions. In many of these cases, metastasis had not been suspected at the time of the clinical examination.

Quinby,<sup>41</sup> in discussing carcinoma of the urinary bladder, has established certain standards in regard to the suitability of a patient for total cystectomy. Among these is an involvement of the floor of the bladder so wide that if the carcinoma were to be treated locally by any method, such treatment would involve the outlet of the bladder to such an extent that loss of vesical function and incontinence would result. There should

40. Spooner, A. D.: Metastasis in Epithelioma of the Urinary Bladder, *Tr. Am. A. Genito-Urin. Surgeons* 27:81, 1934.

41. Quinby, W. C., in discussion of Spooner,<sup>40</sup> p. 92.

be no demonstrable metastasis outside the bladder; in each case, before performing a total cystectomy, he has investigated the retroperitoneal drainage area from the bladder. Frequently, he has been disappointed by finding involvement of the preaortic lymph nodes or of the lymphatic channels leading from the pelvis to that region. The patient is further studied by ordinary roentgenography or by whatever other methods are available to demonstrate secondary deposits. In those instances in which the peritoneum is opened and the retroperitoneal regions are investigated, they are often found to be the site of secondary deposits. It may be possible to treat these regions in a manner similar to that used in treating the axilla in carcinoma of the breast, namely, by dissection, but this is a matter for the future. If it is possible to make a comprehensive dissection of these regions, some benefit may result.

Caulk<sup>42</sup> said that he was studying some 500 cases of neoplasms of the bladder with reference to the upper urinary tract. The study of 300 cases had been completed with reference to the renal involvement, and it was found that the kidney may be involved in three ways: (1) by simple regurgitation from incompetency of the ureteral valve, which is disturbed by the spread of the tumor as it invades the mucous membrane; (2) by stenosis of the ureter, and (3) by extravescical occlusion of the ureter from involvement of the lymph nodes or as a result of superimposed inflammatory reactions around them. In cases in which there was a possibility of invasion because the tumors were situated sufficiently close to the ureter to invade it and to damage the kidney, cystographic studies revealed regurgitation in 24 per cent; in 50 per cent of these cases there was regurgitation without indentures of the wall of the bladder, and in the other 50 per cent there was invasion of the wall. Seventy-eight per cent of the tumors were situated in the region of the trigon, close to the orifices of the ureters. One hundred and forty-four patients were studied with reference to their renal functional capacity as indicated by nitrogenous studies of the blood or by excretory tests, particularly by the phenolsulphonphthalein test. Of these 144 patients, 44 per cent showed *definite diminution of renal function*; 21 per cent of the 300 patients revealed renal infection. There were 90 deaths. In 38 per cent of the cases in which death occurred, there was positive evidence of disease of the upper urinary tract. Twenty-five of these cases came to necropsy: in 60 per cent of these cases, death had been caused by renal disease, a large renal mortality.

Carcinoma of other organs may extend to the bladder. In 400 cases of carcinoma of the cervix uteri, extension to the bladder occurred in

<sup>42</sup>. Caulk, J. R., in discussion of Spooner,<sup>40</sup> p. 93.

3 per cent, and death occurred as a result of renal disease in 50 per cent of these. Whether the tumor is primarily vesical or secondary to extension, the kidney is likely to suffer. The only way to protect the kidney in these cases is by early diagnosis and prompt treatment. In this series of cases, two years and eight months elapsed between the initial symptom and the special study. This condition is improving under medical education.

Weijtlandt<sup>43</sup> reported a case of primary endometriosis of the bladder or adenomyosis vesicalis interna which occurred independently of, and was in no way connected with, an endometriosis of the uterus or adenomyosis uteri interna which was also present. Of the 26 cases of endometriosis of the bladder which have been reported, only 3 belong to the autochthonous or primary variety.

Cases of endometriosis may be divided into two groups: In the first group, there is a direct connection between the normal endometrium and the dystopic endometrial tissue. In the second group, the tumor develops without any direct connection with the mucosa of the uterus. The growths are found in the ovary, round ligament, pouch of Douglas, rectum, cecum, ileum, umbilicus and bladder, and on the serosa of the fallopian tubes and uterus.

Weijtlandt's patient was 31 years of age. She had had profuse menorrhagia since she was 15 years of age. This had not responded to treatment, which had included cuneiform excisions from both ovaries. Her uterus and right ovary, which was cystic, were removed eleven years later. Section of the uterus showed a typical endometriosis which did not extend through the walls or involve the serosa.

However, six weeks after operation new symptoms developed. These consisted of hematuria and painful and frequent urination, which recurred at regular intervals for about three weeks, with an intermission of one week. Cystoscopic examination revealed bullous edema, which extended between the ureteral orifices, just above the interureteric ridge, and at the posterior lip of the vesical outlet. There were several vesicles with blue centers, which looked as if they were filled with blood. A diagnosis of primary endometriosis of the bladder was made, because the endometriosis of the uterus did not even extend through the muscularis and the intervening serosa over the uterus, and the bladder was not involved at the time of operation.

Operation was refused; therefore, roentgenologic castration was attempted to remove the influence of the remainder of the left ovary on the endometrial tissue. This was successful in checking the hemorrhage from the bladder, at first, but there were relapses, and later roentgenologic treatments did not have any effect.

During an appendectomy, attempts were made to remove the remainder of the left ovary, but the excised tissue disclosed only fibrous tissue. Finally, under sacral anesthesia, the endometrioid tissue in the wall of the bladder was fulgurated three times at intervals of ten days. Although enough time has not elapsed to determine whether a permanent cure will be brought about, the result to date has been entirely satisfactory.

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43. Weijtlandt, J. A.: Endometriosis of the Bladder, *Proc. Roy. Soc. Med.* 27:1493 (Sept.) 1934.

In most of the cases which have been reported, the diagnosis has been made after operation and histologic examination. The clinical symptoms and signs which should insure recognition are indicated in the following summary:

(a) Endometriosis of the bladder can be diagnosed only during the period of menstrual activity, not before the beginning of menstruation and not after the menopause.

(b) The disturbances are periodical, coinciding with the menstrual cycle.

(c) In the menstrual period there is frequent painful micturition, and the urine contains albumin and blood. In the intermenstrual period there are no, or only slight, subjective symptoms.

(d) Bimanual vaginal examination may detect a soft swelling, which is tender during menstruation.

(e) Cystoscopy reveals the true nature of the condition. There is swelling of part of the mucous membrane of the posterior wall of the bladder. This locality is explained by the position of the uterus in the case of endometriosis of that organ, and by the mesodermal origin of the trigon, and by the ureteric orifices in the case of autochthonous endometriosis of the bladder.

The treatment of endometriosis of the bladder differs according to the age of the patient. In women who are near the menopause, castration by means of roentgen rays is the simplest method. In women who are young, the most efficient treatment is radical excision of a segment of the bladder. This should always be performed by laparotomy, in order that one may be informed of the relations of the vesical endometriosis to the internal sexual organs and to the peritoneum. If this operation, for any reason, is not feasible, intravesical electrocoagulation may be tried.

*Tuberculosis.*—Thomas, Kinsella and Van Winkle<sup>44</sup> expressed the opinion that the first treatment prescribed in cases of tuberculosis of the bladder should be complete rest in bed, just as in the treatment of other active lesions of tuberculosis. For several years they have used light bipolar diathermy to control tuberculous lesions of the bladder. This was first brought to their attention in endeavoring to control hemorrhage in a tuberculous bladder. The ulcer, or the portion of the bladder which was bleeding, was thoroughly coagulated with bipolar diathermy, by using a weak current with low amperage. Care was taken to produce a superficial destruction of the inflamed, ulcerated area. This treatment

44. Thomas, G. J.; Kinsella, T. J., and Van Winkle, Charlotte C.: Treatment of Tuberculosis of the Urinary Bladder, *Tr. Am. A. Genito-Urin. Surgeons* 27:55, 1934.



not only controlled the bleeding but afforded the patient relief from urinary frequency and from burning and pain at urination. The patient soon requested that this treatment be repeated, because some of the bleeding had recurred and because urination was less painful following treatment than it had been before. This time, in addition to cauterizing the bleeding areas, every inflamed region in the mucosa of the bladder was coagulated. Three or four subsequent treatments were administered. The capacity of the bladder increased, the urinary frequency decreased, and the distress during urination was eliminated.

Subsequently this method of treatment had been used in a large number of cases in which ulcers of the bladder did not respond to the ordinary hygienic methods of treatment. Almost complete relief of the vesical symptoms was obtained in each case, particularly when it was possible to remove the lesion in the kidney, which might continuously reinfect the bladder. Treatment for tuberculosis of the bladder was administered to several patients who had had a nephrectomy but had tuberculosis in the remaining kidney. Rest in bed, plus light coagulation of the inflammatory areas in the bladder, alleviated the symptoms; in some instances, the lesions healed completely. When the patient is a man, the urologist must definitely ascertain that there is no coexisting tuberculosis of the prostate or prostatic urethra. Infection in these structures may prolong the urinary frequency and painful urination, and result in ulcerations in the bladder.

When ulcers of the bladder are treated with bipolar diathermy, spinal anesthesia is advisable. Care should be taken to see that the treatment is always under the direction of the eye. The electrode is not moved around the bladder recklessly. Its end must be in sight at all times before the current is turned on, so that the depth of the coagulation may be carefully controlled. Examination of sections of a bladder that has been treated by diathermy suggests that the cautery tip should not be in contact with the mucosa of the bladder more than a second in any one place. The length of each treatment is limited, so that all the ulcerated areas are not treated at one session. A subsequent treatment should not be given earlier than fourteen days after the previous one. This method of treating tuberculosis of the urinary bladder has, in their experience, given more relief than any other method.

Thomas, Kinsella and Van Winkle<sup>45</sup> suggested certain changes in the usual cystoscopic technic in examinations for genito-urinary tuberculosis. They advised: the use of an anesthesia that will permit painless cystoscopy, with minimal trauma; thorough disinfection of all instruments; proper sterilization of ureteral catheters, and employment of a

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45. Thomas, G. J.; Kinsella, T. J., and Van Winkle, Charlotte G.: *Cystoscopic Technic Necessary for the Diagnosis of Genito-Urinary Tuberculosis*, *Tr. Am. A. Genito-Urin. Surgeons* 27:65, 1934.

careful aseptic technic throughout the cystoscopic examination. A detailed inspection of the prostatic urethra is necessary. Some method should be devised to prevent contamination of ureteral catheters during their passage to the renal pelvis. The amount of ureteral reflux should be determined, and large specimens of ureteral urine should be obtained for inoculation of guinea-pigs. The proper evaluation of differential functional tests with sodium indigotindisulphonate U. S. P. or other dyes is important. Bilateral pyelograms should be made, unless there is some contraindication. These should be inspected immediately, and other pyelograms should be made if the first ones are unsatisfactory. Repeated urologic study is necessary before a complete diagnosis is made and before radical treatment is undertaken.

*Atony.*—Braasch and Thompson<sup>46</sup> said that atony of the bladder is never primary; it is caused by abnormal innervation, by obstruction or by both factors. For the purpose of clinical differentiation, atony resulting from disease affecting the innervation may be regarded as primary. Continuous retention of urine from any cause will produce atony of the wall of the bladder. In some cases it may be difficult to determine which factor is involved. In most cases of atony, obstruction, either primary or secondary, is the predominating factor. The factors which cause sphincteric dysfunction are: imbalance of innervation, with predominance of the sympathetic or filling nerves; rigidity or failure of adequate relaxation of the internal sphincter, which is known as dysectasia, and apparent failure of coordination of the reflexes involved in the act of urination, centering in the neck of the bladder, called achalasia. The first condition can be favorably influenced by presacral neurectomy, and the second condition usually can be remedied by thorough transurethral resection. Knowledge concerning cases in which other causes are operative is insufficient as a basis from which to determine treatment, but in a case of this type which they observed, presacral resection restored function to normal.

The abnormal tissue which interferes with function of the neck of the bladder may in some cases be easily overlooked. It is necessary to remove such tissues completely and to free every cicatricial contraction in order to restore function of the sphincter. Sphincteric abnormality in the female presents problems markedly different from those in corresponding conditions in the male. In most cases, judicious removal of sphincteric tissue will overcome retention, but subsequent presacral neurectomy may be necessary. Localized or partial atony may follow destruction of branches of the nerves of the pelvis in the course of an operation which involves the bladder. Various other types of atony may occur.

46. Braasch, W. F., and Thompson, G. J.: Treatment of the Atonic Bladder. Tr. Am. A. Genito-Urin. Surgeons 27:99, 1934.

In the presence of acute retention, such as frequently occurs following abdominal operation, the advisability of drainage of the bladder before it becomes overdistended should be emphasized. In contrast, in the presence of retention following extensive injury to the spinal column, overflow of the bladder should be permitted rather than to catheterize the patient. It is evident that much remains to be discovered in the mechanism of urination, and concerning the various lesions which may affect it.

*Ulcer.*—Pollak<sup>47</sup> reported 2 cases of simple ulcer of the bladder. Several known factors and the favorable influence of pregnancy suggest that the menstrual cycle is a causative factor in the development and continuation of these ulcers. Local disturbances of the blood supply may also be of importance in producing these simple ulcers or in causing them to recur. Occasionally, a loosely adhering incrustation also may be found attached to the ulcer. Methylthionine chloride U. S. P. (methylene blue) applied locally has been the most successful of the conservative means of local treatment. A study is being made to determine the mode of action of this drug in the treatment of ulcer of the bladder. Of the more radical methods of treatment, fulguration of the ulcer gives the best results.

*Fibrosis.*—Crenshaw<sup>48</sup> reported the late results of panmural fibrosis (Hunner's ulcer) of the bladder. The apparent rarity of this condition was soon discovered to be the result of failure of recognition, and many cases have since been reported. It is not always easy or possible, at the first cystoscopic examination, and in the presence of concurrent cystitis, to distinguish panmural fibrosis from chronic pyogenic areal cystitis; with treatment of the infectious lesions by irrigation, the masking cystitis usually is relieved and pyuria disappears, leaving the cystoscopic picture and persistent symptoms of panmural fibrosis. The symptoms often are so typical that a diagnosis can be made from them alone. These symptoms are: marked urinary frequency, with gradually decreasing capacity and increasing irritability; constant pain, which can often be localized to one area in the bladder and which is markedly increased by a distended bladder; frequent hematuria with distention of the bladder; complete or nearly complete absence of pus in the urine, in contrast with the extreme irritability of the bladder and usually negative culture of the urine.

At present at the Mayo Clinic one type of treatment after another is tried, with overdistention probably giving the best temporary results.

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47. Pollak, Walther: Ueber das Ulcus simplex der Blase, *Ztschr. f. urol. Chir.* 39:362, 1934.

48. Crenshaw, J. L.: Late Results in Panmural Fibrosis of the Bladder, *Tr. Ann. A. Genito-Urin. Surgeons* 27:109, 1934.

Satisfactory overdistention can be performed only with the patient under an anesthetic, and should be done only under observation through a cystoscope, so that the overdistention can be terminated immediately if tears appear in the mucous membrane. Fulguration gives rapid relief from pain, but the pain soon recurs. Following fulguration, as with excision of the lesion, there is often a larger recurrence or multiple recurrences in other parts of the bladder.

Of 123 patients who had panmural fibrosis, 5 were men and 118 were women. Of the women, 93 were married and 25 were single. Forty-five of 47 patients who were treated for this lesion, and who are still living, were females and 2 were males. At the time of the first symptoms, the oldest patient was 61 years of age, and the youngest, 14 years; the average age was 37.4 years. The maximal duration of symptoms when the patient was first admitted for observation was thirty years, and the minimal, three months, and the average was six and six-tenths years.

Treatment of the bladder is not now being taken by 41 patients; regular treatment is being taken by 4, and 2 are taking an occasional irrigation. Temporary improvement occurred in 35 cases, but was absent in 2 cases. Judging from the value for the blood urea or from the excretion of phenolsulphonphthalein, from the results of roentgenologic examination and from the presence of renal pain or renal symptoms, renal disease was not present in any case when the patient was first seen at the clinic.

In evaluating the final results in these cases, Crenshaw considered the patient's statement, as well as the present symptoms and findings, such as frequency, capacity of the bladder, hematuria, pain and general health. Of the 47 patients, 19 were improved greatly or cured; 9 were improved considerably; 6 were improved slightly or moderately. The condition was stationary in 10 cases and worse in 3. In other words, after from five to twenty years, 34 patients were cured or improved, and the condition of 13 was stationary or worse than it was before the treatment was administered.

#### PROSTATE

*Electroresection.*—Cabot<sup>49</sup> said that in recent developments of transurethral resection of the prostate, two types of technic have been used: one may be called the Young-Caulk-Bumpus type; the other, the Stern-Davis-McCarthy type. The former method depends on cutting away portions of the prostate with a circular knife introduced through the sheath, the bleeding being controlled by touching the bleeding points under sight. This involves a minimum of coagulation of tissue. The

49. Cabot, Hugh: The Battle of the Prostates. *Surg., Gynec. & Obst.* 59:682 (Oct.) 1934.

second method depends on the removal of tissue by means of a wire loop charged with a high frequency current. Bleeding is further controlled by direct coagulation. In the first of the two types there is relatively little coagulation, and consequently not as much danger of deep necrosis, which may later be followed by secondary hemorrhage when the slough separates. In the second method, particularly when performed by a less skilled surgeon, relatively large amounts of coagulation may occur, causing the death of a considerable amount of tissue, which is not removed.

These operations have been extensively employed during the last year. The Stern-Davis-McCarthy method has been selected by the majority of operators because the instruments are similar to the cystoscopes commonly used. The Young-Caulk-Bumpus method utilizes instruments with which few even trained urologists are familiar.

The occurrence of accidents in transurethral resection of the prostate emphasizes the necessity of graduate training, even for those who are already expert in the field of urology, and the procedure should not be attempted by others. All the knowledge and experience which have proved essential to successful prostatectomy by other methods are required in the performance of this operation. Technical dexterity in transurethral instrumentation alone will not insure against the complications referred to, nor will it avoid the danger of operating on a patient who is insufficiently prepared. Cabot<sup>50</sup> was of the opinion that the success of this operation will depend on sound training in the surgery of the bladder, on supervised training in the technic of the methods of operation and on a sufficiently large experience to enable the operator to become thoroughly familiar with the technic. Satisfactory results will be obtained only when the operation is performed by qualified experts.

Cabot<sup>50</sup> said that the trend of opinion among the older generation of prostatectomists does not do justice to transurethral resection of the prostate gland. The criteria on which successful prostatectomy should be judged are low operative risk, short confinement in the hospital, complete emptying of the bladder, freedom from lasting infection and permanence of the result. Some of the difficulties in regard to transurethral resection are the result of lack of experience with the operation. A few of the recent reports on this type of operation have been based on a total experience of a small number of cases, an insufficient total to warrant any definite general conclusions.

The case for the transurethral method is strengthened if it is limited to patients operated on by surgeons of equal experience with both types of procedure. Bleeding and infection, the complications reported

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50. Cabot, Hugh, in discussion of Thompson.<sup>51</sup>

in transurethral resection, are those with which prostatectomy of other types has been associated for forty years.

If one limits the discussion to the degree to which the two procedures meet the requirements previously mentioned for successful prostatectomy and to those cases in which the operation is done by experienced surgeons, the results seem to be as follows: The risk and the duration of confinement are less with the transurethral method, and the certainty of complete emptying of the bladder will be found better than with prostatectomy. Although it is commonly believed that all patients whose prostates have been removed "above the bone" empty their bladders completely, such is not the case. A number of patients after prostatectomy have persistent residual urine from which serious and continuous infection results. Tags of mucous membrane, scar tissue which results in bars, and large, stiff-walled cavities are not rare after prostatectomy. In recent years, persistent suprapubic sinuses have become relatively uncommon, but before that they were not rare and indicated failure to remove the obstruction completely. Complete closure of the neck of the bladder after prostatectomy has occurred many times in Cabot's experience. The results of examination of a series of patients two months or so after prostatectomy compare unfavorably with the conditions that obtain after transurethral resection of the gland. The fact that large prostates, particularly in cases in which the enlargement is of the pedunculated type of subcervical lobe, can only with difficulty be managed by the transurethral approach is not an argument against the operation. The experience is sufficient to show that for the average benign obstructing prostate the transurethral approach is the method of choice. The procedure requires special skill and training; it is Cabot's belief that it is an operation which can be satisfactorily done only by the specialist. Patients who have disease of the prostate rarely present any emergency other than the temporary emptying of the bladder. The patient is entitled to the benefits of lower risk and shorter confinement, and the support of prostatectomy because it can be done by the general surgeon is not in the interest of the patient.

Thompson<sup>51</sup> reported that during the four years from Jan. 1, 1930, to Jan. 1, 1934, 37 patients who had dysfunction of the neck of the bladder following prostatectomy were relieved of their symptoms by transurethral resection of the prostate gland. The type of prostatectomy did not appear to be important, for proportionately as many total failures and recurrences followed perineal dissection as followed supra-

51. Thompson, G. J.: The Value of Transurethral Resection in Relief of Dysfunction Following Prostatectomy. *Proc. Staff Meet., Mayo Clin.* 9:546 (Sept. 12) 1934.

pubic enucleation. In a few cases in which the former operation had been performed, urine leaked through multiple fistulas in the perineum instead of through one above the pubic bone. From these data, prostatectomy sometimes resulted in failures other than early postoperative fatality. The mortality of transurethral resection is about a tenth that of prostatectomy. At the Mayo Clinic there was completed a consecutive series of 510 resections in 451 cases, before the next death occurred. In competent hands, incontinence seldom occurs following transurethral resection of the prostate. Cicatricial deformity with resulting contracture following operation that is done with the knife punch is rare. The incidence of recurrence of urinary obstruction because of appearance of adenomatous tissue subsequent to transurethral resection has been only a fraction of the immediate mortality from prostatectomy. Such facts indicate the value of the former procedure.

Kretschmer<sup>52</sup> reported 2 cases in which there were intravesical explosions, which resulted in rupture of the bladder, during transurethral electric resections. In both cases, there was a very small amount of bleeding, and the fragments of the resected prostate were aspirated with the Bigelow evacuator. After aspiration, a few tags were removed with the resectoscope, and it was at this time that the explosion occurred. Kretschmer expressed the opinion that air mixed with the hydrogen that developed during resection, and that this caused an inflammable mixture of gases. One tear was intraperitoneal and one was extraperitoneal. Both of the tears were recognized at once. They were repaired suprapubically, and the patients recovered.

[COMPILER'S NOTE.—Cases of rupture of the bladder also have been reported in the course of fulguration for tumors of the bladder. Cassuto, while fulgurating a median lobe of the prostate with a McCarthy urethroscope, noted a sudden violent explosion inside the bladder. As the bladder did not seem to be ruptured, he waited, ready to operate if peritoneal or other symptoms became alarming. A cystoscopic examination performed on the eighth day disclosed a slightly edematous bladder with large stellate cuts on its surface. Cassuto believed that the gas which accumulated from the carbonization of the tissues exploded. St. Cene, who reported 2 analogous cases, found that the explosion took place on fulguration near the upper surfaces of the bladder, where gas accumulates. In other cases, the bladder has been ruptured without fulguration. The vesical wall frequently is weakened in certain regions as the result of infection, tumors or distention. Most operators while resecting prostatic tissue remove the working element of the instrument following each bite of the loop. This permits an evacuation of the

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52. Kretschmer, H. L.: Intravesical Explosions as a Complication of Transurethral Electro-Resection, *J. A. M. A.* 103:1144 (Oct. 13) 1934.

water in the bladder and also permits the gas which has been generated during that single procedure to be evacuated. If the working element is left in place while several sections are being removed, gas accumulates and the distention with water is much greater. Under sacral anesthesia, overdistention of the bladder from gas or water causes the patient pain, which usually results in relief of the overdistention. Under spinal anesthesia, hazardous overdistention is more likely to occur than with sacral anesthesia. Rupture of the bladder is as much of a surgical emergency as is an acute condition in the abdomen, and delay in operating is as dangerous. It is interesting to note that in most cases in which operation has been done at once, rupture of the bladder has not had undesirable sequelae. Twenty or thirty years ago, almost all cases of rupture of the bladder, regardless of cause, proved fatal. In 1887, Ullman reported only 22 recoveries in 237 cases. In 94 of these cases, the ruptures were extraperitoneal; in 20, the patients recovered. Only 2 of 142 patients who had intraperitoneal rupture recovered. Bartels reported a mortality of 96 per cent in 98 cases in which the condition was treated without operation. Dobrowolskaja and Wiedemann reported 16 cases in which 6 patients were operated on within twenty-four hours from the time of injury; 1 patient (16 per cent) died; the other 10 were operated on in from forty-eight to one hundred and twenty hours after injury; 90 per cent of these died. In 228 (45 per cent) of the 504 cases which were reported by Packmayr, the patients died.]

*Calculi.*—Young<sup>53</sup> classified calculi of the prostate as endogenous and exogenous. The endogenous calculi are those which form within the substance of the prostate, and the exogenous calculi are found in the prostatic urethra; they have developed there in pockets or diverticula, or have reached the urethra from the kidney, ureter or bladder. Young<sup>53</sup> reported 100 cases. In most of these, the calculi were of the endogenous type. These cases may also be divided into those in which adenomatous hypertrophy of the prostate is present and those in which it is not.

A history of gonorrhea was noted in 36 cases (54 per cent) in which calculi of the prostate were associated with prostatitis. In the majority of cases, symptoms of the involvement of the prostate had developed soon after the incidence of the gonorrheal infection, and in many cases these symptoms had continued for years. It generally was impossible to distinguish between the symptoms that were produced by the prostatitis and those that were produced by the calculi. In many instances, the calculi were not recognized, and the patient was treated for a long

53. Young, H. H.: Prostatic Calculi, *J. Urol.* 32:660 (Dec.) 1934.



time for chronic prostatitis, without improvement. The diagnosis of calculi in the prostate usually was made by roentgenography. In only a small proportion of cases were isolated calculi palpable, or was their presence detected by crepitus when pressure was made on the prostate with the finger.

The treatment employed by Young<sup>53</sup> in his cases varied. If the symptoms were negligible, if the prostatic secretion and the urine were sterile, and if the sexual powers were normal, operative treatment usually was not advised and no local therapy was employed. Many of these patients are rather comfortable although their prostates are filled with small calculi. In other cases in which there were pronounced local symptoms, such as irritation, burning, pain, hematuria, difficulty and frequency of urination, marked obstructive symptoms, the effects of back pressure, and pain, operative removal of the calculi was advised.

In 23 cases, adenomatous lobes or hypertrophy of the prostate was present. On rectal examination in cases in which there was prostatic hypertrophy, the calculi were sometimes felt, but the posterior layer of normal tissue of the prostate and the elasticity of the hypertrophied lobes usually made recognition of the calculi by rectal palpation impossible.

Calculi of the prostate frequently produce an induration in the prostate, which is practically identical with that felt in cases of carcinoma. This may lead to an incorrect diagnosis. In discussing diagnostic differentiation of calculi of the prostate from carcinoma of the prostate, Young<sup>53</sup> stressed the value of exposing the prostate by the perineal route, carefully examining it by palpation, making an incision in the suspicious area, removing a section for diagnosis and preparing frozen stained sections, if necessary.

In the cases in which there was a stone in the prostate, calculi were present in the kidney and ureter in 17 instances, and in the bladder, in 6 instances. Certain authors have observed a tendency to formation of calculi in other organs when stones were present in the prostate. Young's statistics do not confirm this assertion, although chemical examination has shown that the same ingredients that are present in calculi of the urinary tract are present in prostatic calculi. Calculi which escape from the prostate into the bladder undoubtedly may form the nucleus of calculi of the bladder, and stones which have come down from the kidney, ureter or bladder and lodge within the prostate may form calculi of considerable size within the prostate.

The exogenous type of calculi in the prostate are rare, and only a few instances of this type are to be found in the records of the Brady Urological Institute. These stones probably do not form within the substance of the prostate. The etiology is perhaps similar to that of calculi of the bladder in the presence of infection. Detritus or bacteria

may form the nuclei of these stones. Exogenous calculi are not true calculi of the prostate.

In 45 per cent of the cases in which calculi of the prostate were associated with benign hypertrophy of the gland, there was a history of gonorrhea. Fifty-four per cent of the patients without benign hypertrophy also gave a history of gonorrhea. In 50 per cent of the total number of cases, there was evidence of chronic prostatitis. In 5 cases, calculi formed within a large abscess cavity in the prostate. Infection undoubtedly is important in the etiology of stones in the prostate. In each of 44 operative specimens studied, localized infection of the prostatic ducts or prostatic acini in the region of the calcification was found. Calculi may form in prostatic ducts or in acini which are blocked with bacterial or epithelial débris. The bacterial and epithelial débris ultimately may form the nuclei of the stones. Corpora amylacea, which commonly are seen in the prostatic acini in the presence of prostatitis, possibly may act as nuclei for calculi.

Imperfect drainage of the prostate, which is caused by contracture of the orifice of the bladder or stricture of the urethra, may inhibit the discharge of secretion and pus from the prostate and, in the presence of infection, may lead to the formation of calculi in that organ. Strictures of the urethra were present in 17 per cent of the cases in which there were benign adenomas and in 13.4 per cent of the cases in which benign adenomas were absent. In many cases, these were not real strictures, but there was urethral narrowing produced by calculi. Obstructions producing retention at the orifice of the bladder were present in 17 per cent of the cases in which there were benign adenomas, and in 18 per cent of the cases in which benign adenomas were absent. Many of these were inflammatory contractures or bars.

*Malignant Tumors.*—Dickson and Hill<sup>54</sup> reported the following case:

A patient, aged 30 years, was well until four months prior to his admission to the hospital for symptoms which led to a diagnosis of tumor in the lower cervical portion of the spinal cord.

His first symptoms had been pain and stiffness in the lower part of the back. This had been followed by weakness of the upper and lower extremities and by anesthesia over the lower part of the abdomen. Spastic paraplegia had followed. This had been associated with paradoxical overflow from the bladder, retention of feces and complete anesthesia of the trunk below the nipple line and of the legs. The intrinsic muscles of both hands showed wasting and other signs of atrophy of the lower motor neuron. An ascending urinary infection developed.

Examination of the cerebrospinal fluid revealed Froin's syndrome, a marked globulin reaction and 3 cells per cubic millimeter. The Wassermann and Kahn

54. Dickson, W. E. C., and Hill, T. R.: Malignant Adenoma of the Prostate with Secondary Growths in the Vertebral Column Simulating Pott's Disease, *Brit. J. Surg.* 21:677 (April) 1934.

reactions of the spinal fluid were negative. Roentgenograms revealed a collapse of the bodies of the seventh cervical and the first thoracic vertebra, and crushing of the three contiguous intervertebral disks, which almost touched each other. There was rarefaction of the body of the second thoracic vertebra and of the transverse processes of the first and second thoracic vertebrae on the right side, as well as of the heads and necks of the first and second ribs on the right side. The roentgenologic findings suggested Pott's disease, with vertebral collapse from softening.

The patient died suddenly, and at necropsy the bony changes were found to be caused by metastatic carcinoma.

The primary tumor was found to involve the prostate, which was only slightly enlarged and the seat of a malignant adenoma.

The case is of interest because of the age of the patient, the silent primary prostatic tumor, the early malignancy in an adenoma, the clinical picture of a tumor of the spinal cord and the roentgenologic findings suggesting Pott's disease.

The bony metastasis was completely osteoclastic and did not show any evidence of the osteoplastic process which is generally described as characteristic of metastasis of a malignant tumor of the prostate to the bones.

Lowsley and Kimball<sup>55</sup> reviewed the literature of sarcoma of the prostate and reported a case of this condition.

The patient was 64 years of age and was admitted to the hospital because of painful and frequent urination and dribbling, which had been present for three years and had increased in severity. Rectal examination revealed a flat prostate, which was of leathery consistency and about two and a half times the usual size. A diagnosis of adenomatous hypertrophy was made, and a suprapubic cystostomy for drainage disclosed a moderate intravesical intrusion. The second stage was not done because of renal insufficiency, and the patient was dismissed from the hospital but was kept under observation for four months, during which time there was no improvement in function of the kidney. He was readmitted to the hospital when it was found that there was an enormous intravesical intrusion of the median portion of the prostate. Excretory urography demonstrated an advanced right hydro-nephrosis and hydro-ureter. There was no excretion of mediums, hence an absence of renal function on the left side. Removal of the prostate was not attempted, and the patient died of uremia two months later.

The anatomic diagnosis at necropsy was leiomyosarcoma of the prostate, bilateral pyonephrosis and bronchopneumonia.

The 132 cases of sarcoma of the prostate which had been reported previously were reviewed and analyzed. Prostatic sarcomas are common to all ages, although 35 per cent occur before the age of 20 years. In young patients, the course is rapid, but when this tumor affects adults, the course is slower, the average duration being nine months. Pain is a prominent symptom. The tumor may grow to an enormous size and cause complications by pressure. Because of its softness, which at times may produce fluctuation, the tumor may suggest a prostatic abscess.

55. Lowsley, O. S., and Kimball, F. N.: Sarcoma of the Prostate, *Brit. J. Urol.* 6:328 (Dec.) 1934.

The tumor invades the bladder, seminal vesicles and rectum, and metastasizes by both the lymphatics and blood stream to the kidneys, inguinal lymph nodes, lungs, liver, pleura and spleen, in this order of frequency.

The disease is invariably fatal, and treatment should be limited to roentgenotherapy and radium therapy to control pain.

*Blood Supply.*—Bumpus and Antopol<sup>56</sup> said that the supply of blood to the prostate gland may be divided into three definite zones: (1) the peripheral plexus of small arteries; (2) an intermediate zone of essentially parallel vessels coursing toward the urethra, where they anastomose to form (3) a zone in which a periurethral or internal plexus is formed. It is evident that in performing transurethral resection the third zone of vessels will be encountered first; they are of large caliber and anastomose so freely about the entire circumference of the urethra that there is no single point at which the bleeding can be entirely controlled. Because of the size and extensive anastomosis of these vessels, bleeding will be more profuse in the periurethral zone than in the deeper, intermediate zone. From a case in which examination was made after operation, it appears that the destruction of the supply of blood may extend well toward the peripheral zone.

#### PENIS

*Carcinoma.*—Horn and Nesbit,<sup>57</sup> in discussing tumors of the penis, said that circumcision in infancy is to be recommended. Early circumcision should be done in all cases of sclerosing balanoposthitis. In all cases in which middle-aged or older persons have been subjected to this procedure and the wound does not heal promptly or within a reasonable length of time, the condition should be regarded as potentially malignant and treated accordingly. The type of operation to employ in the treatment of carcinoma of the penis depends on the nature of the lesion. Radical resection of the regional lymph nodes need not be a routine procedure, even in cases in which there is enlargement of these nodes, because in a great many cases the enlargement is not the result of metastasis but of infection. Emasculation is indicated only in cases in which there is extension to the scrotum or its contents.

Graves<sup>58</sup> said that partial amputation of the penis for carcinoma may be done by any standard method, but the line of incision should be at least 2 cm. proximal to any palpable thickening in the region of the

56. Bumpus, H. C., Jr., and Antopol, William: Distribution of Blood to the Prostatic Urethra: A Demonstration, *J. Urol.* **32**:354 (Oct.) 1934.

57. Horn, K. W., and Nesbit, R. M.: Carcinoma of the Penis with Report of 37 Cases, *Ann. Surg.* **100**:480 (Sept.) 1934.

58. Graves, R. C.: Treatment of Malignant Disease of the Penis, *Tr. Am. A. Genito-Urin. Surgeons* **27**:421, 1934.

growth. The stump of the urethra should be left longer than the stump of the corpora cavernosa; the actual division of the latter is done more satisfactorily with high frequency current. Coagulation controls hemorrhage and lessens the possibility of the dissemination of cells of the tumor.

The technic which Graves used in the treatment of advanced and dangerous lesions is as follows:

There should first be a period of supportive medical care, varying in duration and character with the needs of the individual case. Spinal anesthesia usually is obtained with procaine hydrochloride. Unless the groins are to be dissected, the patient is placed in the position for lithotomy. A vertical suprapubic incision is made in the median line. This extends upward sufficiently so that the scrotum will be drawn well away from the perineum when its upper portion is attached to the apex of this wound at the end of the operation. The lower pole of the incision reaches the base of the penis, where it encircles the organ and penetrates as far as the actual fibrous sheaths of the corpora cavernosa and spongiosum. The corpus spongiosum is then cut across with the high frequency knife, well proximal to the tumor and at a level which will allow sufficient length of the urethra into the perineum for transplantation without tension. A soft bougie then is passed into the open urethra. This aids in dissecting the corpora spongiosum away from the corpora cavernosa. The corpus spongiosum must be freed until it can be brought straight through a small stab wound in the perineum, between scrotum and anus, without angulation or tension. Moist gauze and a wooden spatula are placed between the roots of the cavernous bodies and the bulb to prevent injury of the urethra when the corpora cavernosa are finally amputated near their attachments, with a mildly coagulating current. The open ends of the stumps are closed, either separately or together, with a continuous lock suture of chromic catgut. The stump of the urethra should protrude at least 1 cm. beyond the skin of the perineum at the end of the operation; any redundant portion is cut away. A wick of iodoform gauze is left in one angle of the upper wound for temporary drainage, and the cut edge of the scrotum in the median line is approximated to the apex of the suprapubic incision. Finally, a small soft rubber catheter usually is passed to the bladder and lightly secured to the urethra with a stitch of fine silk or catgut, for the first few days.

The dressings are an important feature of the postoperative care. There always should be a roll or pad in the perineum, in front of the urethra. This is held firmly in place by a perineal binder. It obliterates the newly opened space in the region back of the scrotum and, by elevating the scrotal wall, serves also to protect the suprapubic suture line from undue tension. Whether the inguinal regions are dissected at the time of the amputation of the penis, or at a second operation, the dissection is done through an incision which begins medially to the anterior superior spine and extends parallel with, and above, Poupart's ligament, to within about 1 fingerbreadth of the spine of the pubis, where it curves downward and outward across the femoral triangle. This affords a more adequate exposure than does a simple oblique incision in the groin, and it avoids the poorly healing corners of a T-shaped wound. All palpable lymph nodes and the fat which contains the lymph nodes are removed en masse as far medially as the spermatic cord and the external ring. The dissection must be carried downward over the thigh also, for in Graves' experience a lymph node often is found much farther distally

along the saphenous vein than is expected. A segment of this vein usually will be included in the mass which is removed. Special care must be used to dissect the inner aspect of the femoral vein and the region leading into the crural canal.

High voltage roentgenotherapy directed to the femoral, inguinal and deep pelvic regions should be used in all cases following surgical dissection and in those cases in which, for some reason, such dissection has not been undertaken.

#### URETHRA

*Stricture.*—Young<sup>59</sup> said that it frequently is necessary to pass dilating instruments after various operations which involve the urethra, such as those which are employed for the relief of trauma, inflammatory strictures, urinary incontinence or congenital defects of the urethra. Difficulty may be encountered in passing filiforms through the dense stricture, particularly as they have a tendency to buckle on themselves and prevent the passage of a dilator; the attempt to pass some such dilator often may lead to severe traumatism, if the operator does not realize that the filiform has buckled and broken. New instruments and technical methods which eliminate these difficulties are described. These include a series of urethral tubes which facilitate the discovery of the urethral lumen in the strictured area and also prevent the buckling of the filiform when it and the attached dilator are passed. The use of the catheterizing cystoscope to dilate a stricture of the deep urethra by passing filiforms backward is described. Also various technical devices for joining one filiform to another or for attaching a silk thread or a piece of silkworm gut which is to be left in place to conduct other filiforms through the strictured region at subsequent times are depicted. By means of these mechanical devices, the postoperative care of various urologic patients has been rendered more accurate and satisfactory than it has been in the past.

Caulk<sup>60</sup> reported a series of 1,495 cases of stricture of the urethra. In only 52 of these cases was urethrotomy required; in 2 of these cases the stricture was internal and in 50 cases it was external. In this number of cases, only 2 internal and 10 external urethrotomies were done for uncomplicated stricture, 5 of these having been done prior to 1913. The remaining number were performed for complications associated with stricture, such as extravasation of urine, periurethral abscess, fistulas and impassable stricture. In only 0.8 per cent of all the cases was operation resorted to for simple uncomplicated stricture.

59. Young, H. H.: New Methods of Dealing with Difficult Strictures of the Prostate-Membranous Urethra, *Tr. Am. A. Genito-Urin. Surgeons* 27:19, 1934.

60. Caulk, J. R.: External Perineal Urethrotomy with Invagination and Resection of an Impermeable Stricture of the Penile Urethra, *Tr. Am. A. Genito-Urin. Surgeons* 27:351, 1934.

Caulk<sup>60</sup> reported a case in which there was an impassable stricture of the penile portion of the urethra. Internal urethrotomy was impossible, since no fluid could be introduced, and external urethrotomy at this site was to be avoided. An external perineal urethrotomy was therefore performed.

The bulb was opened in its anterior portion, after the posterior portion of the scrotum had been bisected. The bulbous urethra at this point was tremendously dilated, being at least an inch in diameter; this later aided localization of the stricture. A sound was passed through the external meatus to the stricture at the penoscrotal junction. It was then pushed backward until the obstruction could be seen through the dilated urethra from above. The circular scarred region was then grasped with Allis clamps and invaginated into the bulbous urethra; the sound was gently pushed from the front to aid this maneuver. The segment which was the site of the stricture was then incised vertically until the sound could be passed through it. It was almost a quarter of an inch in breadth. It was then resected circularly until the annular band was completely removed. Before excising this segment completely, the urethral mucous membrane was grasped above and below the sound with Allis forceps, and while the affected segment was being resected, the proximal and distal ends of the urethra were approximated with sutures. Before the sutures were tied, the sound was removed and a no. 24 catheter was passed through the site of the stricture. The sutures were then tied, and a catheter was passed into the bladder for drainage and splinting. After the redundant tissue had been removed, the urethra was closed over the indwelling catheter with interrupted sutures of chromic catgut. A small rubber tissue drain was inserted, and the skin and fascia were closed. The suprapubic catheter was removed and the sinus curetted. The operation was simple in spite of the dense scar tissue. It was not difficult to invaginate the penile urethra into the perineal incision by traction and pressure without mobilization of the urethra through external dissection. The recovery was uneventful.

#### BARTHOLIN'S GLAND

*Carcinoma.*—Lyle<sup>61</sup> expressed the opinion that carcinoma of Bartholin's gland is as malignant as epithelioma of the vulva and, unfortunately, is also resistant to the roentgen rays. He said that the primary operation should consist of a wide excision of the vulva and a secondary dissection of the inguinal and femoral lymph nodes. The excision should be carried out with the cold scalpel or the endothermic knife. In the advanced cases, it is advantageous to destroy the original growth with endothermic coagulation and then proceed immediately with resection. The operation should be followed by thorough local and regional irradiation. Healy, in his cases, applied radon seeds to the recurrence and later did a radical excision of the regional lymph nodes. The success of any method rests on an early diagnosis; this diagnosis is not hard to make if the condition is kept in mind.

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61. Lyle, H. H. M.: Primary Carcinoma of the Bartholin Gland, *Ann. Surg.* 100:993 (Nov.) 1934.

## ANURIA

Joly<sup>62</sup> said that anuria is a symptom of a number of diseases, some of which are primarily unconnected with the urinary tract; it should never be considered as a disease itself. The conditions which cause anuria are so numerous that cases in which this symptom is exhibited are usually classified in three groups: The first one comprises cases in which the abolition of the excretion of urine is the result of some general cause, usually a change in the circulation of the blood. Advanced cardiac disease, a marked fall of the blood pressure or a local interference with the renal circulation are examples of this type, which is known as prerenal anuria. The second type is a renal anuria, and is caused by some change in the renal parenchyma which renders it incapable of excreting urine, poisoning with corrosive mercuric chloride being the most typical example. In the third group, the urine is dammed back in the urinary passages so that none of it can escape; this form is called postrenal or obstructive anuria.

Cases of unilateral anuria are not infrequent. One kidney is completely obstructed by a calculus, but the condition is disguised by the continued secretion from the opposite organ. It is important to recognize these instances, as improvement in the condition of the obstructed kidney depends on prompt removal of the calculus. Unrelieved obstruction always results in the death of the kidney. There are two types of complete anuria which complicate lithiasis: The first is the obstructive type, in which the cessation of excretion is primarily the result of the mechanical action of a stone or stones which block the urinary passages. This form is commonly called calculous anuria. In the second type, there is no obstruction, but the renal parenchyma is so damaged by the presence of calculi, which usually are associated with sepsis, that it is no longer capable of excreting urine. In cases of this nature, the anuria usually is terminal, is unaffected by treatment, and is preceded by a long period in which the patient shows signs of renal failure. Calculous anuria is the most important type of complete anuria occurring with lithiasis, as it is amenable to treatment. The kidneys are not destroyed, but excretion is inhibited, and the kidneys can resume their function once the obstruction is removed. Cases of calculous anuria may be divided into three groups, according to the nature of the obstruction: obstruction of both kidneys or ureters, obstruction of the only functioning kidney and unilateral obstruction. The chief interest in unilateral obstruction is focused about the state of the unobstructed kidney and the reason why it has ceased to function. Formerly, many

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62. Joly, J. S.: Anuria as a Complication of Lithiasis, *Tr. Am. A. Genito-Urin. Surgeons* 27:209, 1934.



cases were described in which the unobstructed kidney was supposed to be healthy, on insufficient grounds. If no stone was found, the organ was assumed to be healthy.

The common and extensive use of the term "reflex anuria" tends to overshadow the fact that the condition depends on the existence of a reflex arc from one kidney to the other, and on whether the unobstructed kidney is inhibited through the nervous mechanism or in some other way. The discussion of reflex anuria has lasted for more than forty years, and as yet there is no consensus. It is now generally accepted that the excretion of urine is essentially a double process: filtration and selective absorption.

Joly was of the opinion that complete anuria following obstruction of one kidney may be explained on the assumption that it is a result of diminution in the general blood pressure, and that a comparatively slight decrease is sufficient when the unobstructed organ is diseased, but a much larger decrease is necessary if it is healthy. This is offered as an alternative to the theory of reflex anuria.

In the cases in which anuria is accompanied by stone, the anuria usually is terminal and is ascribed to renal failure. It is similar to the terminal anuria of chronic pyelonephritis and similar conditions. In these cases there usually is a prolonged febrile period, during which, although a fair quantity of urine is eliminated, the amount of urea in the blood increases slowly, and the usual signs of uremia appear. This is followed by a short period, usually from two to three days, in which the temperature suddenly drops to subnormal, and suppression of urine supervenes. Suppression generally is attributed to renal failure, but in all the cases observed by Joly, it was preceded by a marked decrease in blood pressure. He believed that the suppression is caused by heart failure, and that the treatment should be directed toward reestablishing the circulation. At present, attempts are made to stimulate the kidneys, and this line of treatment always fails. Joly was of the opinion that this form of anuria is caused by circulatory failure, and that it is, therefore, prerenal.

Hinman<sup>63</sup> stated that anuria in the presence of obstruction is commonly explained as either the result of retention, as in cases in which there is complete obstruction, or of cessation of secretion, as in cases of the reflex type, in which there are spasm of the blood vessels and anuria of the secretory type. In experimental work with animals, there are two distinct pathologic changes with complete obstruction of the ureter: In one, there is anuria at the onset, also primary atrophy. In the other, in which there is not anuria, hydronephrotic atrophy occurs.

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63. Hinman, Frank, in discussion of Joly,<sup>62</sup> p. 230.

Hydronephrosis cannot develop with anuria. Therefore, in cases in which complete obstruction of the ureter and hydronephrotic atrophy are present, there is not anuria but retention.

An interesting type of anuria from obstruction in the tubules occurs in association with hemoglobinuria. The hemoglobin crystals, which are precipitated in the blood or in the tubules after the urine is secreted, block the tubules and produce obstruction and anuria. The recognized treatment in these cases is to give large doses of alkali, which dissolves the hemoglobin crystals and reestablishes the urinary secretion.

#### CARCINOMA STATISTICS

Duff <sup>64</sup> reported that all forms of carcinoma caused 125,740 deaths among the industrial policy-holders of the Metropolitan Life Insurance Company, who were aged 1 year or more, in the twelve year period from 1917 to 1928. When related to the more than 174,000,000 years of life recorded for these policy-holders, the mortality was 72.2 per hundred thousand.

Carcinoma of the bladder caused 3,315 deaths, 2.6 per cent of the total deaths from all types of carcinoma in this twelve year period. A higher mortality from carcinoma of the bladder was registered for white males (2.6) than for white females (1.5). The higher rate for males was in evidence at each significant age period. Among the colored race, the males showed a higher mortality than the females; the rates were 2 and 1.3, respectively. White men suffered a higher mortality than did colored men, but among women the element of color was insignificant. The death rate from carcinoma of the bladder rises continuously with advancing age; practically no deaths occurred from this lesion among persons under 25 years of age.

Carcinoma of the prostate caused 1,904 deaths in these twelve years. This is only 1.5 per cent of the deaths from all malignant growths. The death rate for white and colored males was identically the same (2.5 per hundred thousand). The mortality from this disease also rises with increasing age, but the mortality is not significant before the age of 55 years. The mortality at the various age periods for white persons was close to that registered for colored persons. The trend of the death rate from carcinoma of the prostate appears to be upward since 1917. Among colored males the increase was considerably more than it was among white males.

The death rate from carcinoma of the kidneys and suprarenal glands in the period from 1917 to 1928 was 0.8 per hundred thousand. The number of deaths was 1,332, or 1.1 per cent of the entire mortality from

64. Duff, John: Cancer Mortality: Bladder, Kidney and Prostate. 1917 to 1928, *J. Urol.* **32**:346 (Oct.) 1934.

carcinoma in this period. Of the 1,332 deaths, no less than 313 (23.5 per cent) were those of persons between the ages of 1 and 25 years. The death rate at this age period was 0.3 per hundred thousand. The figures for the different sexes show little difference. The death rate for white persons of each sex is practically double that for the colored. The age curve differs from the usual carcinoma curve in that no rise is shown between the earliest age group and the one following (from 25 to 34 years); also, the rise with increasing age is not as sharp as for most types of carcinoma. In general, the frequency of this type of carcinoma in the last five years of the period appeared to have changed relatively little in comparison with that for the preceding five years.

#### ANESTHESIA

Jeck<sup>65</sup> reviewed a series of cases in which spinal anesthesia was induced with nupercaine in the low dilution of 1:200, and compared this with a series of cases in which a dilution of 1:1,500 was employed. Satisfactory anesthesia was induced with the weaker solution in 90 per cent of the cases and with the stronger solution in 68 per cent of the cases. In a group of operations below the umbilicus, in which practically any spinal anesthetic would have given relatively satisfactory results, the percentage of successful anesthetics with the dilute solution was slightly higher than that with the concentrated solution.

Vomiting, headache and distention occurred about equally after the use of the concentrated and dilute solutions of nupercaine. Vomiting depends on the level to which the anesthetic extends. This is substantiated by the fact that in the operations above the umbilicus vomiting occurred in a third or more of the cases in which either the concentrated or the dilute nupercaine solution was given; the percentage of cases in which vomiting occurred was slightly higher with administration of the dilute solution than with that of the stronger solution. Headache, one of the most troublesome of the sequelae of spinal anesthesia, is not encountered any more frequently after spinal anesthesia induced with nupercaine than after that produced with other drugs.

With both the dilute and the concentrated solutions of nupercaine, the respirations are usually shallow and regular; respiratory failure is an ever present danger. If respiratory failure occurs, a mixture of carbon dioxide and oxygen should be forced into the lungs by means of an inhalation apparatus. Respiratory failure is less likely to occur from phrenic paralysis than from fatigue of the respiratory center, which is caused by the anoxemia resulting from imperfect pulmonary ventila-

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65. Jeck, H. S.: Nupercain as a Spinal Anesthetic with Special Reference to the Employment of Nupercain Solution of High Dilution, *Tr. Am. A. Genito-Urin. Surgeons* 27:411, 1934.

tion, which, in turn, is the result of temporary paralysis of most of the intercostal muscles. The administration of carbon dioxide and oxygen should rapidly restore regular breathing, unless the respiratory center has already been paralyzed by large doses of morphine, tribromethyl-alcohol (avertin) or similar drugs.

#### POSTOPERATIVE HEMORRHAGE

Weil<sup>66</sup> said that it is of the greatest importance to the urologic surgeon to determine, before undertaking an operation, the tendency of the patient to bleed. If, instead of the usual bleeding, a massive hemorrhage occurs, the patient's blood is at fault. Hemorrhages can be prevented, since most abnormalities of the blood can usually be corrected. To this end Weil proposed four methods of investigation:

1. A study should be made of the coagulative qualities of the blood *in vitro* (method of Hayem). In this test the blood is always taken from a vein at the elbow and not drawn from the tissues; this prevents possible contamination that might interfere with coagulation and thus obscure the true facts. The examination should reveal whether coagulation is normal, retarded, diminished or absent. The color of the serum should be observed, and the retractile function of the coagulum and possible autolysis should be noted.

2. The number of platelets should be determined (method of Pagniez and Lesourd), as well as the proportion of platelets in comparison to the erythrocytes. This interesting test may be omitted, however, since the other three tests are sufficient.

3. A study should be made of the purpura that is produced experimentally by the tourniquet test (as described by Frugoni of Italy and by Weil and Chaliér of France). In cases in which there is weakness of the capillaries, petechiae remain; that is, the tourniquet test is positive. It is absent, however, in cases of hemophilia.

4. The duration of experimental bleeding should be determined (as described by Duke). The size of the drops received on filter paper also should be observed. In cases in which the blood is normal, the size of the drops diminishes after a known time. In cases in which there is a hemorrhagic tendency, the size varies and the rhythm of the drop is entirely irregular. Coagulation, if excessively retarded, is conclusive proof of hemophilia, which is always accompanied by diminished retractibility of the coagulum and by plasmatic coagulation. The provocation of purpura by arrest of venous circulation, the irretractility of the coagulum and the marked diminution of platelets form a characteristic syndrome of

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66. Weil, P. E.: Les hémorragies post-opératoires: Comment les prévoir et les prévenir? *J. d'uro.* 38:289 (Oct.) 1934.

pathologic hematogenesis. It is, of course, possible, even in the presence of abnormal function of the blood, that not all tests are indicative of the disturbance; one test may be negative. This depends partly on the nature of the disturbance and partly on the general state of the patient. The causes of a tendency to bleed are:

1. Hemophilia, a rare disease, which usually is inherited, but may appear sporadically and affect persons who are not members of hemophilic families. In either case, the hemorrhage is the result of provocation, although the hemorrhage is less serious in the sporadic cases.

2. Hematogenesis, which has frequently been confused with hemophilia. It differs from the latter in that the hemorrhage may be provoked, or, again, it may be spontaneous. These subjects show weakness of the capillaries, prolonged duration of bleeding and troubles of coagulation without notable retardation of coagulation.

3. Hepatism, which is prone to affect patients and gives the same signs as vascular disease does. Knowing the cause of these signs to be disease of the liver, and less serious than diseases of the blood vessels, the surgeon may, however, anticipate the possibility of hemorrhage and act accordingly. The clinical examination, the history and the tests which have been described will reveal whether or not a patient possesses a tendency to bleed. Weil has shown that postoperative hemorrhages are preventable. For almost thirty years, he has demonstrated that the inability of coagulation in hemophilia can be corrected in vitro by the action of serum, and that retarded coagulation can be corrected in vivo by injection of serum. Such injections of serum have not proved satisfactory in the treatment of other conditions, because of the possibility of anaphylaxis. In the treatment of these conditions hematotherapy gives excellent results. In the evening before the operation, from 10 to 15 cc. of blood should be injected subcutaneously, without regard to different groups of blood. This treatment is sufficient in nearly all cases. In the presence of hemophilia, however, a transfusion of about 300 cc. of blood from a universal donor, or from a donor belonging to the same group, is recommended. This preparatory hematotherapy gives assured results. No other method is as satisfactory. If there is time, calcium may be prescribed for a long period; this will lessen capillary weakness. It is not to be regarded as a substitute, however, but merely as a complement to the methods described before, which give to the surgeon the means of successfully preventing postoperative hemorrhages.

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## FASCIAL SARCOMA AND INTERMUSCULAR MYXOLIPOSARCOMA

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The term fascial sarcoma became established in reports in the older German literature (1850-1900) but never gained wide usage. Virchow<sup>1</sup> described fascial sarcoma as *occurring rather frequently*, especially in the superficial fasciae of the lower extremities. It was generally of fibromatous or fibrosarcomatous structure, but sometimes it was quite cellular and malignant and therefore probably of rather uncertain nature and origin. In many cases there was formation of cartilage and bone, and Virchow seems to have identified this fascial sarcoma with the so-called parosteal sarcoma. He remarked that osteosarcoma is not necessarily a bone sarcoma. He did not use the term fascial sarcoma for any of the intermuscular myxosarcomas. He fully described intermuscular myxosarcoma, occurring especially in the thigh but also in other regions where fat tissue is abundant. He did not state the exact origin of intermuscular myxosarcoma, but he noted the frequent presence of fat cells and of fat tissue in the tumor, which he seems to have regarded as the fatty degeneration of a primary myxoma. Cartilage and bone were found occasionally in intermuscular myxosarcomas, but because of this he did not identify the myxosarcoma with the true fascial tumor containing cartilage and bone.

Later authors confused intermuscular myxosarcoma with the true fascial sarcoma described by Virchow. Thus Hellmann<sup>2</sup> in 1888 analyzed eighty-three cases of sarcoma of the inguinal region, reporting seven cases as instances of fascial sarcoma. Six of the tumors were cellular growths of the type of myxosarcoma. They were located between the deep muscles and were attached more or less to the deep fasciae, to the muscles or to the sheaths of blood vessels. The exact origin was not determined. The other tumors of the series arose from nerve trunks, muscles, lymph nodes and miscellaneous sources. Hellmann referred the origin of many inguinal sarcomas to the sheaths of vessels.

From the Memorial Hospital for the Treatment of Cancer and Allied Diseases.

1. Virchow, R.: *Die krankhaften Geschwülste*, Berlin, A. Hirschwald, 1863, vol. 2, p. 342.

2. Hellmann, L.: *Ueber den Ursprungsort der Weichteilsarcome der Region inguinalis*, Würzburg, H. Stürtz, 1888.

In 1913 Massenbacher<sup>3</sup> reported several cases of intermuscular myxosarcoma, especially in the thigh, and referred the origin to the deep fasciae and the fascia lata. Apparently he did not recognize that the tumors were quite different in location and structure from the fascial tumors described by Virchow. Most of the cases reported in the literature to which he referred were instances of desmoid tumor of the abdominal parietes. In the recent literature, the term fascial sarcoma does not appear frequently. In the "Quarterly Cumulative Index Medicus" for the past ten years I find references to only two cases of the condition. One of these was a case of enchondroma of the subcutaneous fascia reported by Goldmann<sup>4</sup> in 1928. The other was a case of perithelial sarcoma of the cubital fossa above the elbow following alleged trauma described by Cooper<sup>5</sup> in 1930. Although the median and internal cutaneous nerves ran through the tumor, they were apparently not connected with its origin, and the author concluded by exclusion that the tumor must have arisen from the deep fasciae.

At the present time the term fascial sarcoma, if used at all, is generally applied to the intermuscular myxosarcomas described by Hellmann and by Massenbacher and to desmoid tumors of the abdominal wall and not to the fibrous, fibromatous, fibrosarcomatous or parosteal sarcomas described by Virchow. It is to this former group of myxosarcomas that the present study is directed.

Notwithstanding the paucity of reports, deep intermuscular tumors of this type are not rare. On the contrary, they form a well defined clinical group of malignant tumors of the extremities, of which the gross anatomic changes are uniform and characteristic, the structure peculiar and highly specific and the clinical course progressive and generally fatal. Surgical intervention is generally unavailing, and the therapeutic problem is therefore urgent. If a definite histogenetic origin could be established, these tumors could be regarded as a specific neoplastic disease.

As a result of a study of many tumors of this type over a period of years and of a comparison with other deep intermuscular sarcomas in the same regions, I have reached the conclusion that the characteristic intermuscular myxosarcoma sometimes referred to as fascial sarcoma is a variety of liposarcoma in which the small blood vessels are the predominant element and in which mucous tissue, instead of fat tissue, is the product of the cell growth. This conclusion might well have been drawn from the descriptions given by Virchow and the early observers, who often noted the abundance of fat cells in a few of these tumors.

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3. Massenbacher, J.: Fascien-tumoren, Beiträge z. klin. Chir. 88:69, 1913.

4. Goldmann, D.: Zentralbl. f. Chir. 55:2379, 1928.

5. Cooper, T. V.: Lancet 2:1234 (Dec. 6) 1930.

but when the term fascial sarcoma came to be employed for the group, the idea of an origin from fat tissue seems to have been neglected.

#### POSSIBLE SOURCES OF ORIGIN OF INTERMUSCULAR MYXOSARCOMA

As possible sources of such tumors muscles, nerve trunks, muscular fasciae and fat tissue must be considered. While some myxosarcomas contain cartilage and a few others have shown bone formation, the theory of an origin from misplaced islands of periosteum seems to have no definite evidence in its support, although an osteogenic influence from the proximity of the tumor to bone might be considered as a possible, but rather intangible, explanation. The tumors are not connected with bone, and the bone shaft is not affected even by pressure, as are certain neurogenic sarcomas lying near bone. The occasional presence of cartilage and bone must be ascribed to a metaplastic process.

The possibility that the origin is from muscle must also be rejected. A myosarcoma of the skeletal muscles arises within the muscle and not between the muscles. While muscle fibers are sometimes found in myxosarcomas, this seems to occur exclusively in rare cases in which the myxosarcoma, usually encapsulated, breaks the capsule and infiltrates the skin and neighboring tissue. This event occurs only in the later stages of a recurrent tumor. The structure of the tumor also is entirely different from the large spindle cell and giant cell composition of a myosarcoma.

Neurosarcoma presents myxomatous features in a small proportion of cases, but in such cases the other features of the growth reveal characteristic signs of neural origin. On dissection, nerve trunks may be seen coursing through the myxosarcoma, but usually the nerves are readily separated from the tumor. The structure of intermuscular myxosarcoma is quite different from that of myxomatous neurosarcoma. Yet combinations of neuroma and lipoma are not extremely rare, and occasionally one encounters a malignant tumor of the nerve trunks composed of myxomatous and liposarcomatous elements. Such a growth was described by Virchow in 1857.<sup>6</sup>

A direct connection between the myxosarcoma and the fasciae investing the muscles I have not observed, and it does not appear to have been demonstrated in any reported case.

The fasciae investing the voluntary muscles appear in the form of strands of dense fibrous tissue radiating from the tendinous insertions and condensed into firm, tough flat bands in particular regions. Its structure is that of very dense avascular fibrous tissue resembling tendon tissue. Such tissue cannot be regarded as a ready source of any tumor process. The true fascial tumor is therefore quite rare. That any

6. Virchow, R.: Virchows Arch. f. path. Anat. 11:281, 1857.



of the soft vascular myxosarcomas arise from true fascial tissue investing the muscles seems highly improbable and lacks any definite support. The term fascial sarcoma should be limited to the fibromas, fibrosarcomas, chondromas, osteomas and parosteal sarcomas described by Virchow and by a few later writers.

*Origin from Sheaths of Vessels.*—The older authors were much impressed with the evidence suggesting that some intermuscular sarcomas arise from the walls of the deep blood vessels. On surgical dissection the tumors were found to arise from a pedicle consisting of a leash of blood vessels; some were very vascular and contained cavernous blood spaces, with the multilobed mass closely adherent to the fasciae and to the walls of the vessels. Hellmann collected reports of nine cases in which the tumor was thus connected with the vessels, but the histologic details in these cases were inadequate to determine the exact nature of the tumors. He was therefore unable to establish the exact point of origin, and he quoted Langenbeck as stating that a definite indication of origin of any of these tumors from the sheaths of blood vessels could not be given. The gross description of the tumor suggests that it was really a form of myxosarcoma or liposarcoma in which the central nutrient blood vessels were unusually well defined. If the tumor arose from a lobule of fat tissue, the overgrowth of central blood vessels would explain the vascular character of the tumor and also the close connection with the sheaths of blood vessels.

*Origin from Fat Tissue.*—In considering the origin of intermuscular myxosarcoma from fat tissue, one must refer to the general physiology, embryology and structure of fat tissue. Schaffer<sup>7</sup> emphasized the close relationship of fat tissue, cartilage and chordal tissue, any one of which may substitute for or replace any other under comparable conditions, as is shown by comparative histologic study. In this connection, reference may be made to the report by Seidelin<sup>8</sup> of the occurrence of chordoma-like cells in a liposarcoma lying between the pectoralis major and the pectoralis minor muscle. According to Fleming, fat tissue cells arise regularly and probably invariably from fixed connective tissue cells, and fat tissue is therefore to be closely identified with connective tissue. On the other hand, Toldt separated fat tissue sharply from connective tissue and held that it is derived from well defined lobulated embryonal organs located in various regions in which fat tissue normally appears in the adult. In these organs there is a rich, peculiar and closed system of fine blood vessels in the meshes of which lie specific round granular cells without membrane which become the fat cells of adult fat tissue. The last-mentioned

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7. Schaffer, J., in von Möllendorff: *Handbuch der mikroskopischen Anatomie des Menschen*, Berlin, Julius Springer, 1929-1930.

8. Seidelin, H.: *Acta path. et microbiol. Scandinav.* 9:289, 1932.

conception is of importance in the present connection, because many types of myxosarcoma and liposarcoma have this structure and therefore lend support to this opinion. Myxosarcoma, especially, in the early stages exhibits first a striking overgrowth of fine blood vessels, arterioles and capillaries about which fat cells and mucous material develop. The cells, steatoblasts and lipoblasts, are derived from the adventitial layers of the blood vessels. They first appear as granular nucleated cells lying in the rich capillary network and producing a structure which resembles liver tissue. This structure is often suggested in cases of cellular liposarcoma.

Mucous tissue often appears in an embryonal fat anlage, the cells assuming the shape of stars and lying in a scanty mucinous matrix. This same structure is more often observed in regressing fat tissue, and it is closely imitated in myxosarcoma.

The adult fat cell is surrounded by a membrane the composition of which somewhat resembles elastic fibers. Besides fat, the cell always contains a nucleus, flattened and generally invisible in sections of the tissue. A trace of granular cytoplasm accompanies the nucleus, and in it a Golgi apparatus has been identified. In regressing and inflamed fat tissue the granular cytoplasm increases, and the nucleus enlarges, becomes visible and multiplies; thus the alveolar structure of inflamed fat, familiar to all pathologists, is produced. The same changes with granular polyhedral cells containing little fat often appear in the early stages of liposarcoma.

Histologists emphasize the existence of two kinds of adult fat: the common white fat and the less widely distributed brown fat. Brown fat is found chiefly in the mediastinum, the perirenal region and the axillae and about the thymus and the joints. The cells are large, polyhedral and granular, and they contain varying proportions of fat granules, sometimes only a few. The tissue is therefore opaque and highly colored. This structure is observed in fatty tumors and is generally designated by pathologists as xanthomatous. Yet all xanthomatous processes can hardly be considered to develop from brown fat tissue. The occasional occurrence of an orange-colored lipoma or liposarcoma, especially about the joints, kidneys and adrenals, suggests that the origin is from brown fat.

This short review of the comparative histologic and embryologic characteristics of fat tissue supports the view that intermuscular myxosarcoma is a form of liposarcoma and is derived from fat tissue. This tumor reproduces exactly the early embryonal process of fatty development by the growth of adventitial cells in a network of small blood vessels in a mucinous matrix. The tumor cells usually fail to experience their normal development into fat cells and remain in the

mucinous stage, but not always. The final proof of the origin from fat tissue is furnished by the observation of several cases collected over a period of years, in which typical myxosarcoma without a trace of fat was associated with typical cellular lipoma or liposarcoma (fig. 3).

#### ANATOMIC AND HISTOLOGIC CHARACTERISTICS OF FAT TISSUE IN THE SITES OF ELECTION OF MYXOSARCOMA

In a series of fresh cadavers and amputated limbs, dissections were made of the fat tissue about the knee, hip, elbow and shoulder in order to obtain any possible data that might bear on the origin of fatty tumors in these regions, which are the main sites of intermuscular myxosarcoma. The study did not prove very profitable. Abundant fat pads were found between the muscles, especially about the hip and Scarpa's triangle and in the buttocks. They filled the spaces between the muscles but were entirely free from the muscle investments and fasciae and from the subcutaneous layers of fat and were continuous with the periarticular masses of fat. They ensheathed arteries, veins and nerve trunks. In the upper part of the thigh there was a notable admixture of small nerve trunks coursing through the fat. The blood vessels were very abundant, especially large veins with muscular walls resembling sinusoids of the adrenals.

Microscopic sections threw no light on the origin of the tumors. Yet the deep fat pads contained many more small arterioles than are found ordinarily in depot fat. These tissues did not escape the inroads of the diseases from which the subjects died, such as arteriosclerosis, thrombosis, periarteritis, leukemic deposits, lymphocytic infiltrations and varicosities. No evidence of the effects of trauma was observed, but slight fibrosis and regression of fat were noted in emaciated elderly subjects. As an anatomic source of myxosarcoma in the regions studied the fat pads were entirely adequate, and no other source of origin could be suggested. No definite areas of brown fat were encountered except possibly about the knee joint. Deep lipoma lying between the muscles of the extremities was not infrequently observed.

#### CLINICAL ASPECTS

Intermuscular myxosarcoma occurs chiefly in middle-aged married women but also in males at nearly all ages after infancy. A history of trauma has not been noted in the present cases, but trauma is not infrequently alleged to precede true liposarcoma. The tumor begins as a painless swelling of the deep tissues and grows steadily but not rapidly, usually reaching a large bulk before demanding the attention of the patient (fig. 1). The tumor is firm but not as firm as ordinary

liposarcoma and not hard like neurosarcoma. Owing to the depth of the tumor, the whole limb may be uniformly swollen. Attempted excision of the tumor usually is partly successful owing to the encapsulation of the outlying lobules, but the deeper portions are difficult to reach and recurrence is nearly constant. The tumor then fungates through the operative scar and becomes infected and necrotic, and the patient dies from severe sepsis. The tendency for distant metastases to occur is less than in the case of most other types of cellular sarcoma.

The encapsulated multilobulated tumor lies between and, as a rule, does not invade the muscles, but recurrent growths breaking the capsule

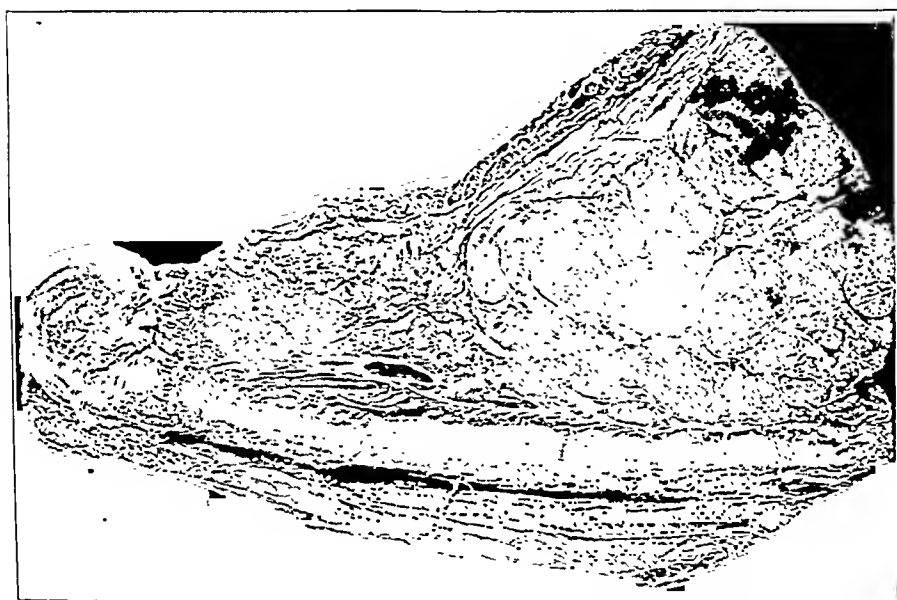


Fig. 1.—Gross anatomy of an intermuscular myxosarcoma of the thigh.

may invade freely the muscles, the fat tissue and the skin. The texture is that of smooth elastic mucous tissue, moderately vascular and without much tendency to necrosis.

Section shows a peculiar and highly characteristic structure, composed of a fine network of capillaries or small arterioles and supporting mucous material in which are a few round or spindle cells, not very hyperchromatic. Fat cells are generally missing, but in the few cases mentioned there has been a considerable admixture of lipomatous tissue of the small cell embryonal type. The cells seem to be derived entirely from the adventitial or endothelial cells of the blood vessels. The process must therefore be interpreted as a capillary or arteriolar angioma, with excessive mucus or occasional production of fat. It reproduces the

process of the formation of fat in the embryo as described by Schaffer and others.

The common liposarcoma occurs in the same locations and presents much the same clinical features, but usually it is more rapid in course, firmer, more prone to yield pulmonary, cutaneous and general metastases and equally dangerous to life.

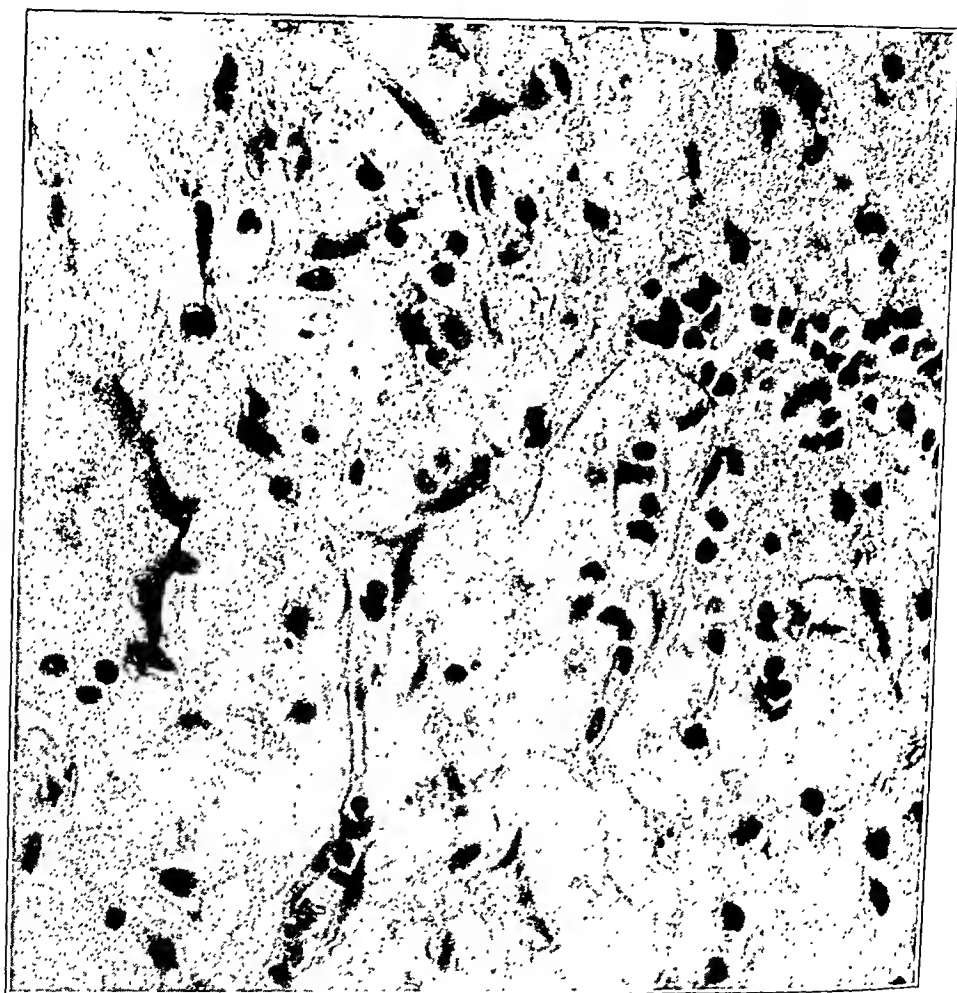


Fig. 2.—Detail of the structure of a myxosarcoma. All the proliferating cells seem to be derived from the walls of capillaries.

Yet the structure of the common liposarcoma is entirely different from that of myxosarcoma. It shows a diffuse growth of large or small polyhedral granular cells in which the proportion of fat globules diminishes with the grade of anaplasia. It presents a wide variety of structures, from diffuse, perithelial and alveolar sarcoma to very anaplastic, malignant, hyperchromatic, indifferent round cell sarcoma. Foci of fat cells are commonly found in some areas. Mucous degeneration may be present, but never to the extent seen in myxosarcoma. I

have not found combinations of granular cell liposarcoma and myxosarcoma. The two processes seem to be notably distinct.

On the basis of the data mentioned one may recognize the existence of two types of liposarcoma. One is composed of granular cells derived from adult fat cells, growing first within the cell membrane as in chronic inflammation of fat tissue and later becoming diffuse and appearing in many grades of anaplasia and malignancy, but not marked by any primary growth of blood vessels and not tending to produce mucous tissue. It represents the lawless phase of the growth of fat

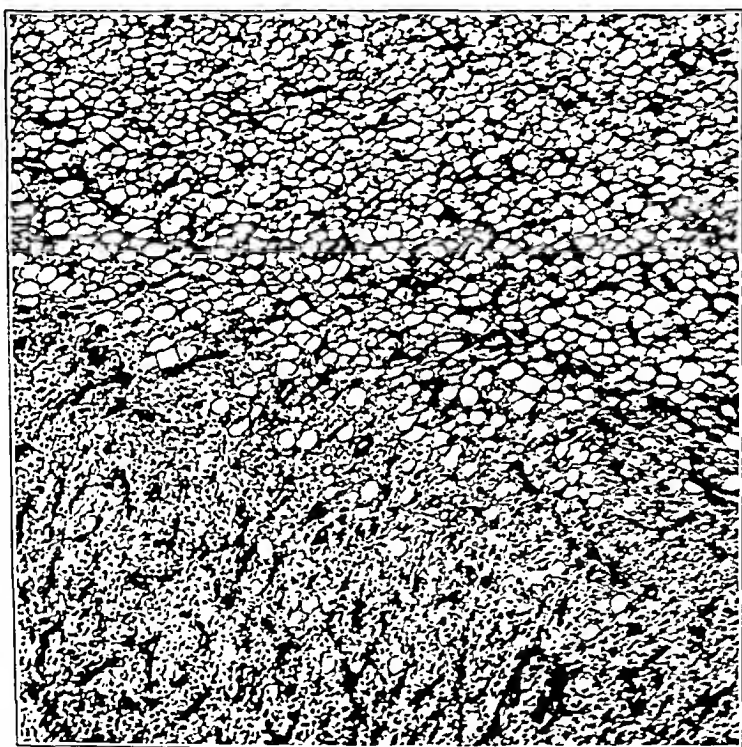


Fig. 3.—Photomicrograph showing the structure of a myxoliposarcoma. Capillaries and mucous tissue are seen in one part and embryonal fat tissue in another.

cells observed in lesser degree in chronic inflammation of fat tissue. It may be called the adult form of liposarcoma (figs. 4, 5 and 6).

The other type of tumor follows the process of the embryonal growth of fat tissue and begins with the proliferation of capillaries and arterioles, the adventitial or endothelial cells of which, instead of going on to produce fat, yield chiefly mucus and occasionally embryonal fat tissue. This variety may be called embryonal liposarcoma or, on account of its anatomic relations, intermuscular myxoliposarcoma.

## TREATMENT

The almost uniformly fatal outcome of liposarcoma and myxosarcoma of the extremities presents a melancholy picture and raises the question whether a more accurate recognition of the nature of



Fig. 4.—Photomicrograph showing an early stage of myxosarcoma from an outlying focus of a tumor about the knee joint.

these tumors and their unfavorable clinical course and the use of nonsurgical methods may not give better results. The decision in this question is a matter for cautious clinical judgment and experience. However, it may be stated that many forms of liposarcoma and of

myxosarcoma are radiosensitive, sometimes extremely sensitive. The structure of myxosarcoma with its fine capillary blood vessels suggests the source of the high radiosensitivity which has sometimes been exhibited by this tumor. The blood supply of primary liposarcoma and myxosarcoma seems to be delicately balanced and easily affected by high voltage irradiation. On recurrence neither of the tumors, how-

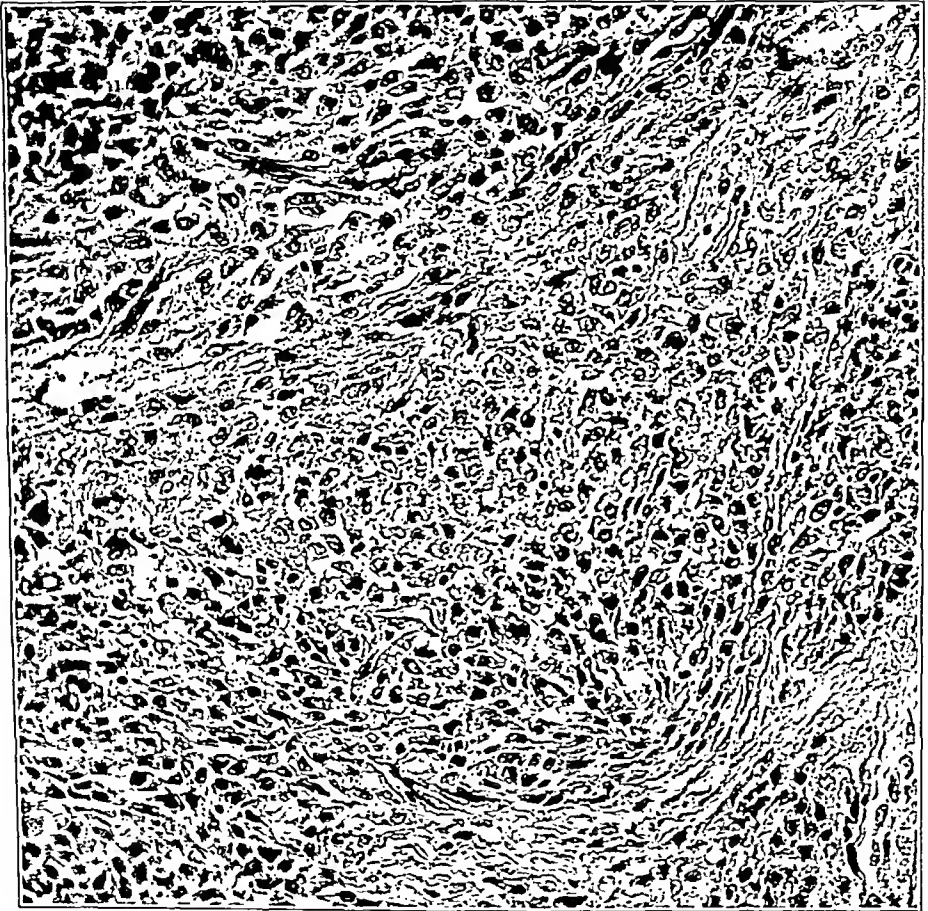


Fig. 5.—Photomicrograph showing the structure of an adult liposarcoma. Note the opaque granular cells. Many fat granules were demonstrated by sudan III.

ever, shows the same radiosensitivity, probably for the reason that the blood supply of the recurrent tumor is obtained from peripheral sources and not from one central system, since the tissue of the recurrent tumor on being released from any capsule grows diffusely.

I was sharply impressed by this fact in a case of a tumor in the early stage which was observed in 1915:



The patient was a middle-aged woman who on presenting herself at the Memorial Hospital had a bulky tumor of the false pelvis and another bulky tumor of the thigh, which had recurred after operation. The structure was that of a myxosarcoma. The larger tumor of the pelvis disappeared rapidly under irradiation with the old Müller x-ray tube, which delivered about 125 kilovolts. The tumor on the thigh resisted similar treatment completely and fungated through the scar; it became infected, and the patient died as a result of sepsis. At autopsy the remains of the pelvic tumor were found as a flat mass of fibrous tissue covering the iliopsoas muscle.

Since most other forms of deep sarcoma of the limbs and of neurosarcoma, myosarcoma and osteogenic sarcoma recur after operation, and

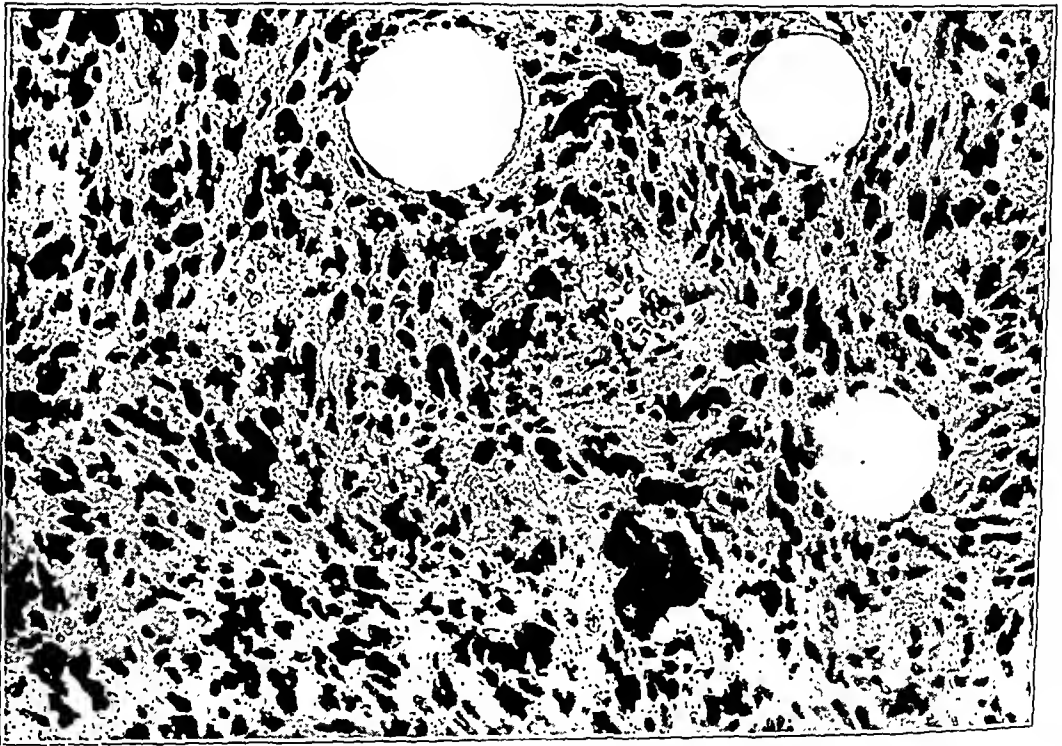


Fig. 6.—Photomicrograph of a highly malignant adult liposarcoma.

since some are radiosensitive, I venture to suggest that the primary treatment of all bulky deep sarcomas of the extremities, especially those of the thighs, arms and axillae, should be by irradiation, external or interstitial or both. With this policy some of the radiosensitive tumors might be controlled or cured. Others would doubtless resist, but the results could hardly be worse than those secured under the present surgical mode of attack.

#### ETIOLOGY

No special exciting factors can be discerned in the clinical histories of most of the patients with intermuscular myxosarcoma. The great majority of the tumors arise without any clinical indication of extraneous

factors. The occurrence in the same situation of lipoma, neurofibroma and mixed neurolipoma indicates that the incitement to growth must be spontaneous in the sense that the growth of all lipomas and neurofibromas is spontaneous or dependent on ill defined abnormalities in structure or nutrition of the affected region. The occurrence of many chronic lesions in the fat pads of the thigh as part of the manifestations of general diseases of the body has already been mentioned.

A history of trauma has frequently been given by patients presenting intermuscular sarcoma, but the importance of trauma must be accepted with caution, since the majority of patients give no hint of any trauma.

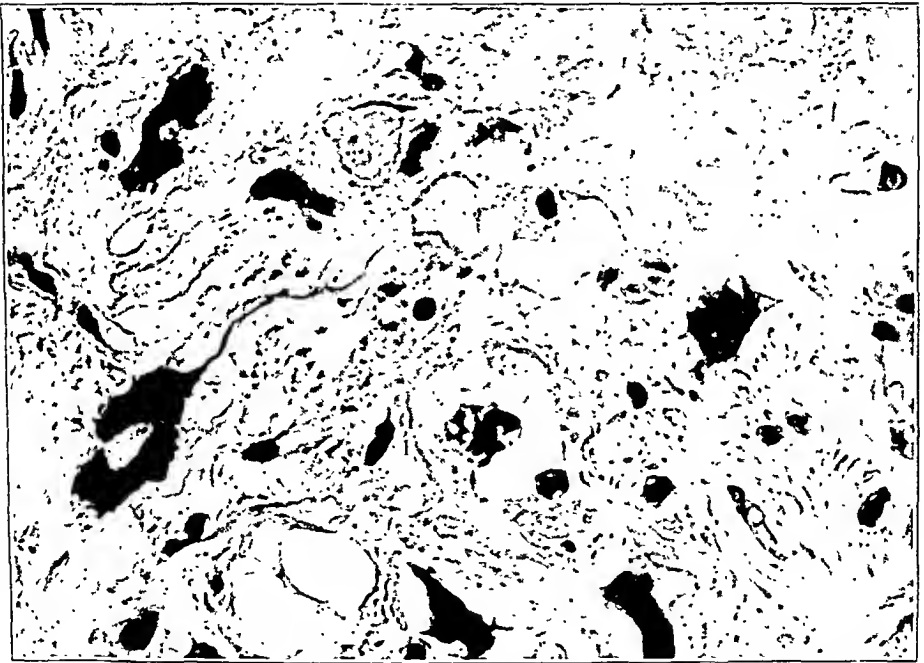


Fig. 7.—Photomicrograph of a degenerating fibrosing but malignant adult liposarcoma.

A history of trauma is a most definite and reasonable explanation for the origin of tumors of the subcutaneous fat tissue and of the adult form of liposarcoma rather than of the embryonal type.

In the following case a traumatic origin seems to be reasonably well established for a low grade liposarcoma:

A highly intelligent middle-aged woman stated that she was in the habit of striking her right thigh against a projecting corner of a bureau in passing from one room to another in her apartment. After many such mild bruises she noticed a persistent tender swelling in the subcutaneous tissue, which slowly increased for several months. The mass was then excised. The material removed was a mass

of subcutaneous fat tissue, 3 by 4 cm. in diameter, the central portions of which were opaque, soft and cellular. On section, the opaque portions consisted of a diffuse growth of adult fat cells, with granular cytoplasm, hyperchromatic nuclei and the general structure of a beginning liposarcoma of moderate but definite malignancy. There was no recurrence.

Reviewing a series of histories of cases of liposarcoma of the adult type, I have been somewhat impressed by the frequency with which a definite history of severe trauma with resulting hemorrhage has preceded the appearance of the tumor at the point of injury. Since traumatism to fat tissue is often followed by marked proliferation of fat cells and progressive productive inflammation, it is not unreasonable to assume that under special circumstances the proliferation may take on a malignant character, especially in the subcutaneous layers of fat. That similar trauma can affect the deep fat pads of the thigh is much less acceptable. On the other hand, it is clear that these deep fat tissues are much exposed to chronic trauma by stretching, straining and muscular compression, to which, rather than to any single trauma, the incitement to growth might be referred.

#### SUMMARY

The term fascial sarcoma should be restricted to the fibromas, fibrosarcomas, fibrochondromas or parosteal osteosarcomas originally described and designated as fascial sarcoma by Virchow. It should not be employed for intermuscular myxosarcomas.

The intermuscular myxosarcoma, often called fascial sarcoma, is probably derived from fat lobules and presents the structure of embryonal mucous tissue or embryonal fat tissue. It is rarely, if ever, of traumatic origin and is often radiosensitive.

The common liposarcoma of the trunk and limbs is derived from adult fat tissue and presents the structure of large granular cells such as those seen in chronic inflammation of fat tissue. The structure varies greatly with the degree of malignancy. It seems to be occasionally of traumatic origin. The degree of radiosensitivity of the primary tumor is uncertain, but the recurrent tumors are radioresistant.

It appears that two types of liposarcoma may be recognized, one the myxoliposarcoma of embryonal structure and the other the granular cell liposarcoma of the adult type.

Liposarcoma of both types is comparatively common in the region of the hip, knee, shoulder and trunk. It runs a characteristic clinical course, usually recurring after operation and proving fatal from infection, sepsis and metastases to the lungs. Since some are radiosensitive, it is recommended that all bulky tumors of the soft parts be submitted to treatment with high voltage irradiation before resort to surgical intervention.

# ANAL DUCTS

## COMPARATIVE AND DEVELOPMENTAL HISTOLOGY

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AND

C. ALEXANDER HELLWIG, M.D.

WICHITA, KAN.

The large rôle in anal disease which is played by the crypts of Morgagni is generally recognized. According to Rankin, Bagen and Buie,<sup>1</sup> infection of these structures is the underlying factor not only of cryptitis, anal fissure, periproctitic abscess and anal fistula but also of hemorrhoids. Our own microscopic studies<sup>2</sup> of more than four hundred proctologic specimens demonstrated that the crypts of Morgagni were not by themselves responsible for the frequency of anal infection but that infection originated as a rule in preformed tubules which we called anal ducts. They were found to open into the crypts, affording a ready path for infective organisms from the intestinal lumen into the wall of the anal canal.

While the pathogenic significance of the anal ducts was thus established, the question presented itself whether these structures have a definite function or whether they represent a vestigial organ. We hoped to obtain some information regarding the nature of the anal ducts by studying embryonic and comparative anatomic material. The present paper is based on histologic studies of the anal region in the dog, cat, guinea-pig, rabbit and chicken and of longitudinal sections of six human embryos.

In textbooks the anatomic fact is not sufficiently stressed that the rectal mucosa with its Lieberkühn crypts does not join directly with the epidermis of the anal canal but that a circular zone, varying in height from 0.5 to 1.2 cm., separates the entodermal and the ectodermal portion. Its epithelium is composed of several layers of polygonal cells, while the superficial cells are columnar. It is only from this transitional epithelium of the intermediate zone that we have found the anal ducts to originate and extend into the submucous or muscular layers of the anal canal (figs. 1 and 2).

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From the Department of Surgery and Pathology, St. Francis Hospital.

1. Rankin, F. W.; Bagen, J. A., and Buie, L. A.: *The Colon, Rectum and Anus*, Philadelphia, W. B. Saunders Company, 1932.

2. Tucker, C. C., and Hellwig, C. A.: *Histopathology of Anal Crypts*, Surg., Gynec. & Obst. **58**:145, 1934.

The histologist who receives a small section from the intermediate zone of the anal canal without knowing the exact source will hesitate to diagnose it as part of the intestines; rather he will take it to be a section of the urethra with para-urethral ducts. So striking is the resemblance between the intermediate zone of the anal canal and the derivatives of the urogenital sinus that a developmental relationship between these two structures seems obvious.



Fig. 1.—A longitudinal section through the anal canal in man. The intermediate zone (C) is between the entodermal and the ectodermal portion. The anal ducts, opening into C, are well developed. (Microscopic section by courtesy of J. E. Pritchard, Montreal, Canada.)

We examined, first, the anal region of several animals. Of the mammals, the rabbit (fig. 3), the dog and the pig have in the intermediate zone complex glandular organs which seem to have a definite, probably sexual, function by producing odoriferous substances. Still more interesting were our observations in fowls. The wall of the cloaca in the chicken is surrounded by a voluminous gland. During the first year of life, this glandular organ is embedded in dense lymphoid



Fig. 2.—A section showing a branching of the anal duct. The epithelium is transitional and stratified columnar.

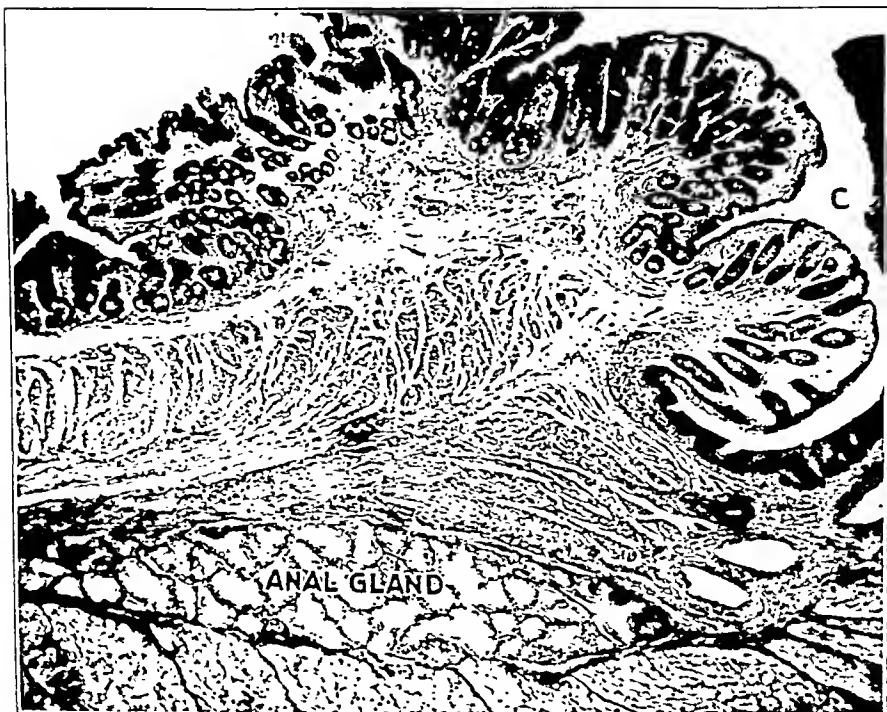


Fig. 3.—A large anal gland in a rabbit which seems to have a sexual function. The mucin stain gave negative results. The excretory duct opens into the intermediate zone of the anal canal (C).



Fig. 4.—The cloacal gland of a chicken. It is homologous to the prostate, para-urethral and anal glands of higher animals.



Fig. 5.—A longitudinal section through a human embryo 0.5 cm. long. The fetal cloaca (C) is connected with the lower end of the rectum (R) and is closed off from the outside by the cloacal membrane.



Fig. 6.—A longitudinal section through a human embryo 18 mm. long. The cloaca has become divided into the urogenital sinus and the intermediate zone of the anal canal (C). The anal membrane, which is a remnant of the fetal cloacal membrane, is still intact.



Fig. 7.—A section through the anal region of a human embryo 32 mm. long. Three well formed anal ducts are developing from the transitional epithelium of the intermediate zone (C).





Fig. 8.—The anal canal of a new-born infant. *C* indicates the derivative of the fetal cloaca. Several well formed ducts open into the intermediate zone.

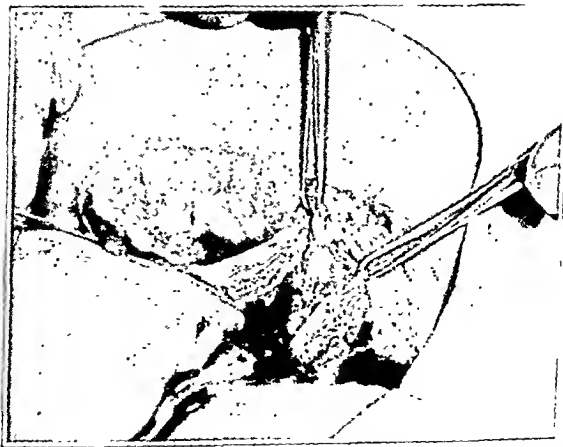


Fig. 9.—An infected anal duct disclosed during an operation for anal fistula. The fistula originated from this duct. The upper forceps is held in the same direction as the infected duct.

tissue. Our own studies failed to elucidate the function of this large cloacal gland, nor does the newest monograph on the anatomy of *Gallus domesticus*<sup>3</sup> contain any pertinent data. The fact, however, that this gland has been called the anal, prostate or Cowper's gland by zoologists indicates that the anal, prostate and para-urethral glands of mammals are homologous to this cloacal gland in the fowl (fig. 4).

The development of anal ducts was studied in six human embryos of different age. The youngest was 0.5 cm. long, which would cor-



Fig. 10.—An infected anal duct with leukocytes in the lumen and in the wall. The epithelium is preserved in many areas.

respond to an age of 3 weeks. The work of Johnson<sup>4</sup> was confirmed. The rectum in the earliest stage presented at its lower extremity a spindle-shaped swelling which extended into the fetal cloaca. The cloaca was closed off from the outside by the cloacal membrane (fig. 5). The division of the cloaca into the urogenital sinus and the

3. Calhoun, M. L.: The Microscopic Anatomy of the Digestive Tract of *Gallus Domesticus*, Iowa State College J. Sc. 7:261, 1933.

4. Johnson, F. P.: The Development of the Rectum in the Human Embryo, Am. J. Anat. 16:1, 1914.

rectum takes place in embryos about 15 mm. long. When the cloaca becomes divided into dorsal and ventral parts the dorsal half of the fetal cloaca becomes incorporated with the rectum and forms the intermediate zone of the anal canal (fig. 6). In embryos about 30 mm. long we found distinct anal ducts arising from the upper portion of the zona intermedia (fig. 7). All were distinctly tubular and gave off several branches at various levels. The glandular ducts extended sometimes through the internal sphincter and terminated in the connective tissue between the muscle layers. The epithelium of these ducts was stratified



Fig. 11.—Infected prostatic ducts with leukocytes in the lumen and within the transitional epithelium of the wall.

and columnar and, in the branches, became cuboidal (fig. 8). In our human material the development of the anal ducts took place at the same time as did that of the prostate and the para-urethral ducts. The latter originate from the urogenital sinus, a derivative of the anterior portion of the cloaca.

Our conception that the intermediate zone of the anal canal and the urethra are derivatives of the same fetal organ, namely, the cloaca, and that the anal, prostate and para-urethral ducts are homologous structures was further substantiated by pathologic observations. Figures 9, 10,

11 and 12 show a striking resemblance between infected anal prostate and para-urethral ducts. All three structures are often involved in gonorrheal infection. Martin<sup>5</sup> pointed out recently that in gonorrheal infection of women the anal canal also becomes infected in about half the cases. In our own series of cases of infected anal ducts, 22.1 per cent were caused by the gonococcus. The transitional epithelium of the intermediate zone of the anal canal, with its anal ducts, apparently furnishes the same favorable biologic conditions for the *Neisser* coccus as do the other derivatives of the cloaca. And the same rôle which in

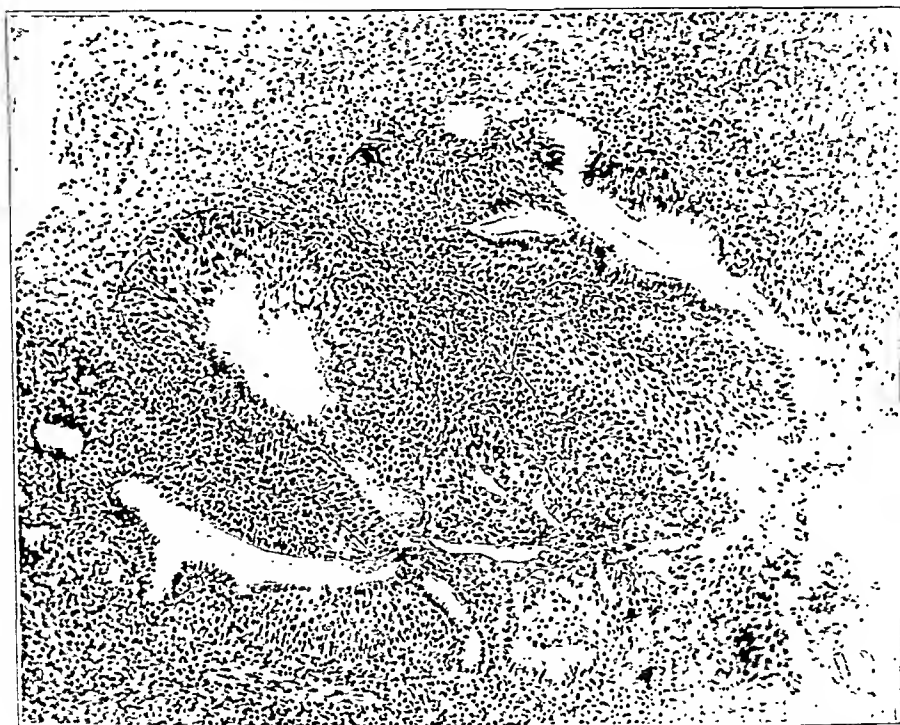


Fig. 12.—Infected para-urethral ducts with leukocytes and plasma cells in the wall and surrounding the ducts. Gynecologists call this condition urethral caruncle.

reinfection is played by the prostate and para-urethral ducts by harboring the gonococcus is played by the anal ducts.

#### CONCLUSIONS AND SUMMARY

Anal ducts are preformed tubular structures which open into the crypts of Morgagni. Infection of these ducts is responsible for so-called cryptitis, anal fistula and periproctitic abscess.

5. Martin, C. L.: Rectal Contamination in Women, *J. A. M. A.* **104**:192 (Jan. 19) 1935.

In human embryos the anal ducts develop at the same time as the prostate and para-urethral ducts. The intermediate zone of the anal canal and the urogenital sinus are derivatives of the same fetal organ, i. e., the cloaca.

In the chicken a large cloacal gland is found which resembles the prostate, para-urethral and anal ducts of higher animals. The rabbit, dog and pig have complex glandular organs in the intermediate zone of the anal canal which seems to have a sexual function.

The anal ducts in man are vestigial remnants of these large glands.

From a pathologic point of view, the anal ducts have much in common with the prostate and para-urethral ducts. All three play an important rôle in gonorrheal reinfection by harboring the gonococcus.

# FIBROSARCOMA OF THE RIGHT FOREARM WITH EXTENSIVE GROWTH INTO THE CEPHALIC VEIN

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CHICAGO

The following case is reported on account of the rarity of sarcoma, especially fibrosarcoma, in the veins occurring as an extension of sarcoma in their vicinity and not as true metastasis.

## REPORT OF A CASE

*History.*—A. S., a man aged 42 years, married, with four living children, was apparently in good physical condition except for a tumorous lesion extending from the right wrist to the forearm (fig. 1). This lesion was first observed about eight years before examination, and started as a small lump near the palmar surface of the wrist; there were no symptoms of pain or any inflammation. The swelling gradually and slowly increased until about one and one-half years before examination, when it was observed to be spreading up the forearm; it finally extended from the wrist to the biceps. On examination it was seen that on the flexor surface and radial side of the right forearm there was a superficial swelling with two red areas. The original site of the swelling at the wrist became reddened about four years before examination, and there was another reddened area higher up on the forearm.

The patient's history was irrelevant. He had the usual diseases of childhood and had gonorrhea and syphilis. The abdomen and other areas were normal. There was no history of traumatism.

*Examination.*—The tumor appeared very vascular with some telangiectatic areas on the older nodule. There were two distinct nodules. The smaller, older, movable nodule was located over the right wrist joint and extended into the palm and about one-third the distance up the forearm; on its surface there were two or three distinctly hyperemic areas. The main mass was firm, hard and rounded, and there were seven small radiating nodules which could be felt extending from the surface. The second main nodule was of more recent origin, freely movable and compressive; it did not appear to be so vascular as the first and was less firm. A longitudinal tail-like extension spread along into the flexor surface of the arm (fig. 2). No other swollen areas were found in the vicinity or elsewhere, nor was there any suggestion of such. The lymph glands of the axilla were not enlarged.

From the clinical data it seemed that the condition was of the nature of a progressive, fibrous or cartilaginous process of the subcutaneous tissue process of a benign character.

The roentgenologist reported a large, soft tumor of the right forearm, which appeared to be of lymphatic origin, with an irregular linear type of calcification in the lower part of the mass; there was no involvement of either the radius or the ulna (fig. 3).

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Read before the Western Surgical Society, St. Louis, Dec. 7, 1934.

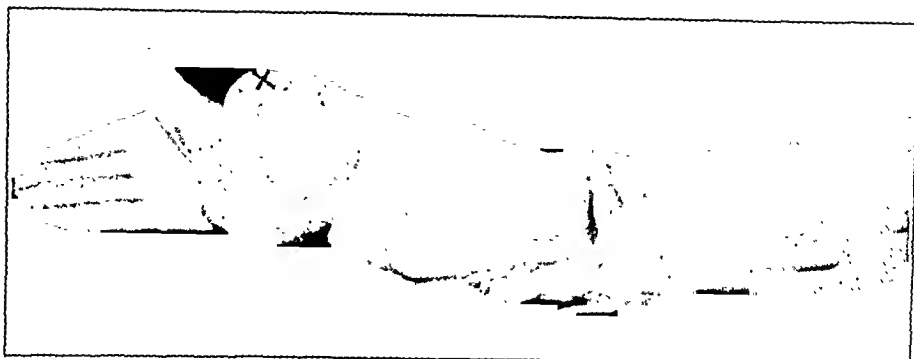


Fig. 1.—The appearance of the growth on the volar surface of the forearm.

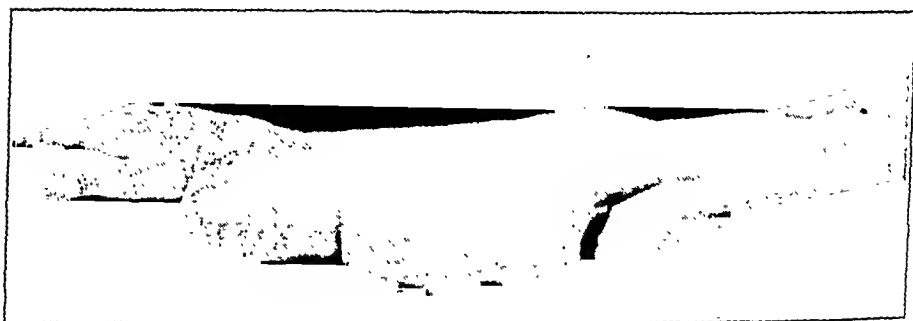


Fig. 2.—The extension of the growth on the radial side of the forearm with extension upward within the cephalic vein.

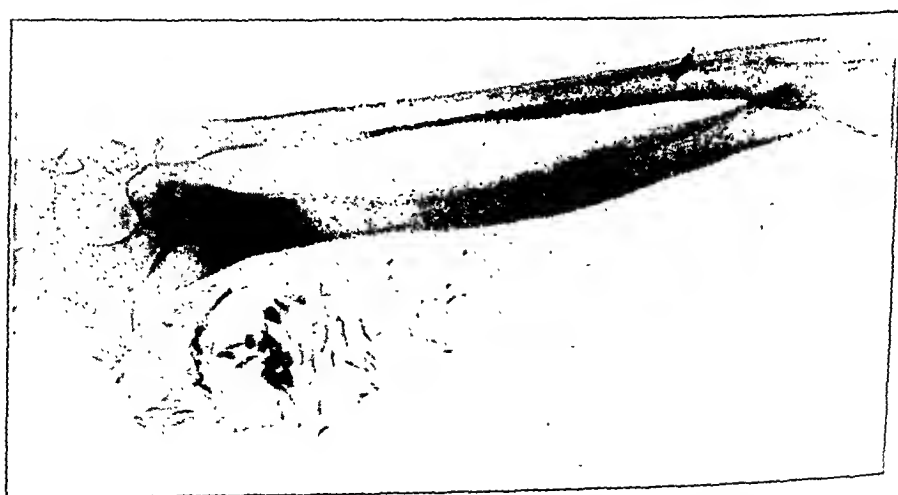


Fig. 3.—Roentgenogram of the forearm showing the two masses, one at the wrist and the other higher up on the forearm. In the lower mass especially are seen areas of calcification which most probably resulted from hemorrhage into the tumor.

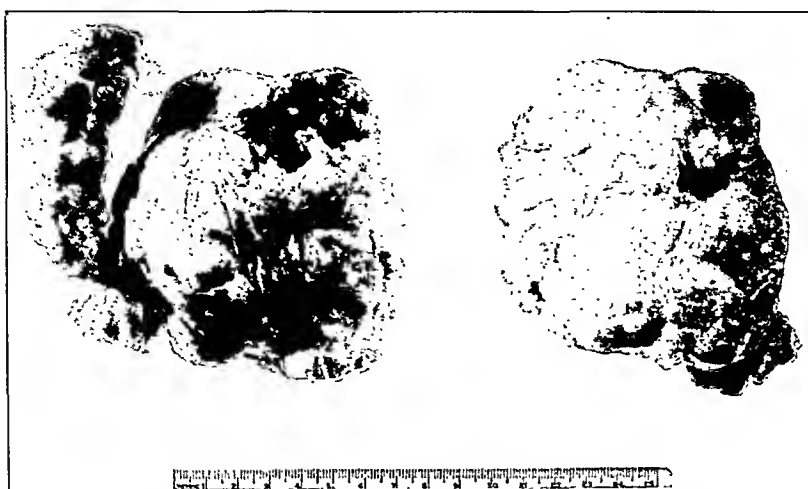


Fig. 4.—The lower mass, near the wrist.

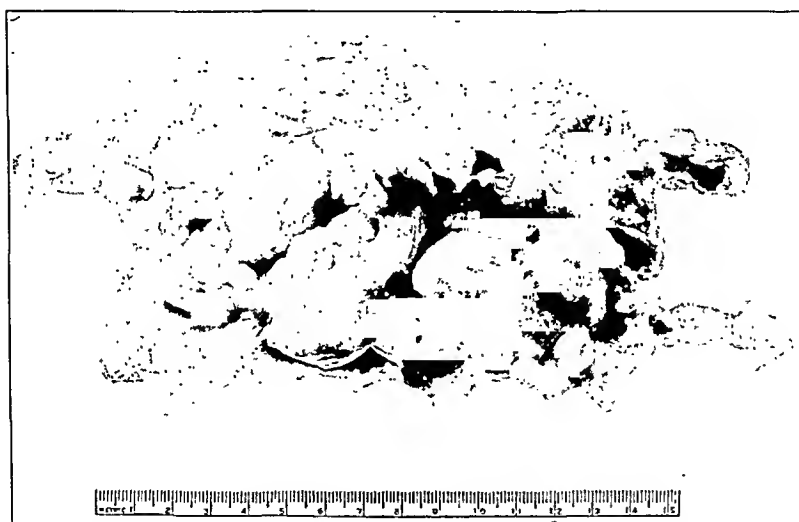


Fig. 5.—The upper mass, near the elbow joint.

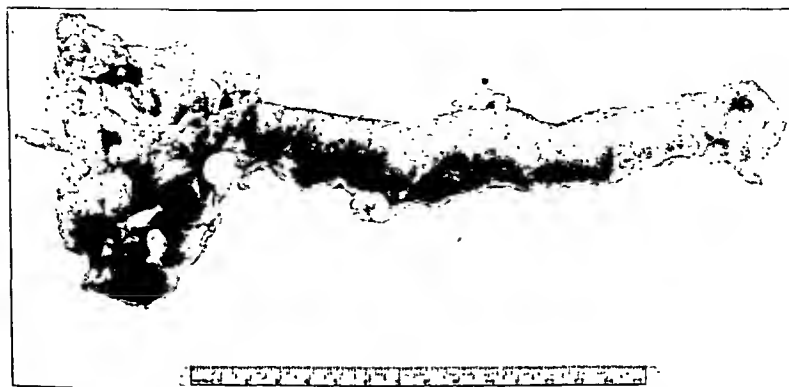


Fig. 6.—The tumor extending upward in the cephalic vein.



No definite diagnosis could be arrived at from the evidence at hand, and it was determined to make a biopsy on material from the original part of the growth; removal of this material caused profuse hemorrhage. It was then decided to excise the masses with the patient under gas anesthesia.

*Operation.*—The tumor was found to be an invasion of the blood vessels (veins) of the forearm, dilating them considerably, especially the median cephalic vein. The growth had invaded or replaced some of the muscle tissue, especially the palmaris longus muscle, but it had not involved the bones. The mass consisted of large nodules which were friable. In the distal part there were some areas

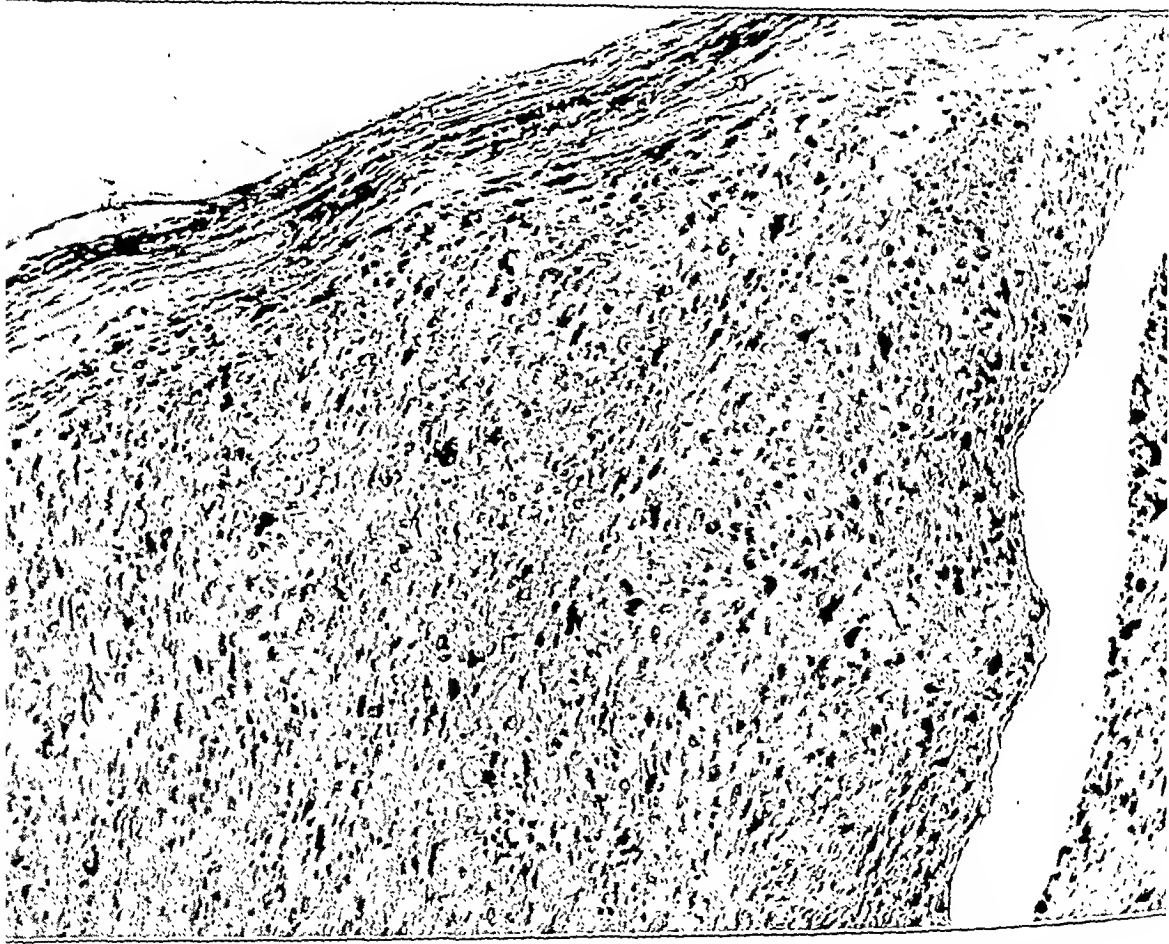


Fig. 7.—A photomicrograph of the tumor with the wall of the vein at the top. A typical intratumor blood vessel is seen near the right edge. The large amount of fibrils and fibers is evident from the distance between the fibroblastic tumor cells.

of calcification. The mass was dissected away from the surrounding tissues, and with careful hemostasis there was very little bleeding. Following removal of the constrictor muscle no pulsation could be felt in the radial artery, and the hand and arm were cold and lifeless. It was therefore decided to amputate the lower third of the arm 7 cm. above the elbow, which was accordingly done.

The two tumors were 7 and 9 cm. in diameter, respectively; the larger one was embedded in muscle and fascia, and surfaces made by cutting were uniformly

gray except for the heavier stroma coursing here and there so as to produce a trabeculated appearance. The extremity from which the tumor had been excised on being dissected showed extensive invasion by masses of similar tumor tissue which apparently were intimately related to the peripheral nerves.

*Histologic Examination* (by Dr. E. R. LeCount).—The growth belonged to the group of fibrosarcomas for which the old term desmoid is still occasionally employed, growths more commonly encountered in the broad ligaments of women and in the subcutaneous tissues of the trunk or sides of the neck. They are rare in the back wall of the trunk but occur frequently in the lower half of the

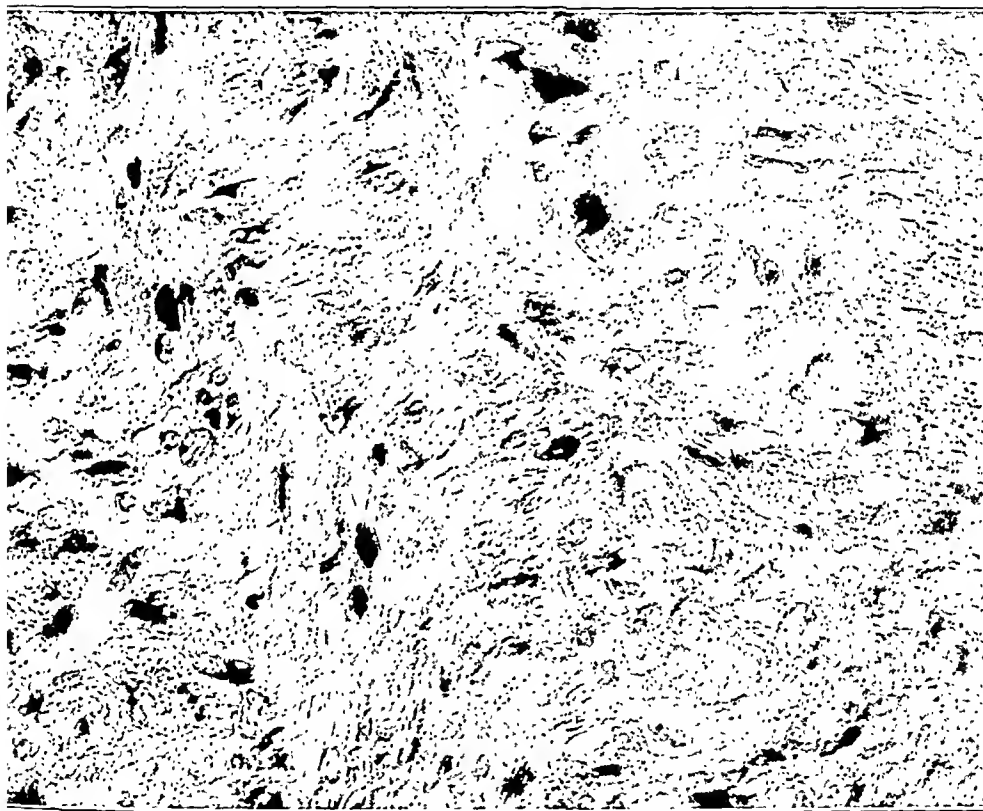


Fig. 8.—A photomicrograph showing the relative amount of the tumor tissue occupied by fibers and by the cells from which they arose. On the right and near the top are a few masses of aggregated nuclei resembling giant cells.

abdominal wall. They are much less malignant than fascial fibrosarcomas of, for example, the thighs. Occasionally they recur after removal and then usually grow more rapidly.

As a rule, they have a thin capsule and grow in an expansile fashion. One removed several years ago by Dr. Kellogg Speed<sup>1</sup> grew in the upper part of the abdominal wall on the right side and passed through its capsule to invade the

1. Speed, Kellogg: Tumor of Chest Wall, S. Clin. North America 10:213 (April) 1930.

abdominal cavity, liver and diaphragm just below the costal arch but produced no secondary metastatic growths. When these tumors give rise to secondary regional or distant separate metastatic growths it is after the sarcomatous element has become more dominant in new tumors which appear after the primary ones are removed.

The nuclei of the tumor cells were far apart (fig. 8), and the intervening tissue was full of fibers which stained blue with aniline blue and both blue and yellowish with phosphotungstic acid and hematoxylin. All the stages of development of fibrils, reticulum and the heavier collagen bands were readily followed in sections of high magnification in preparations suitably stained.

In many places the nuclear material was in masses so that multinucleated cells were simulated, but without any uniform pattern. The blood vessels all had thin walls (fig. 7), and there was nothing left of the wall of the vein surrounding so much of the growth (fig. 7) to indicate its character. In some sections there were small edematous regions.

From the foregoing observations there appears to be no doubt that the tumor was a fibrosarcoma of the veins of the forearm.

#### COMMENT

Tumors of the veins are fairly rare. They may be primary or secondary, benign or malignant. Independent sarcomatous masses in the veins, whether primary or secondary, are very rare, and textbooks such as those of Ewing,<sup>2</sup> Ribbert,<sup>3</sup> Bland-Sutton<sup>4</sup> and Borst<sup>5</sup> give little attention to them; Nothnagel, in his "Specielle Pathologie,"<sup>6</sup> mentioned them especially as secondary carcinoma.

Among the reports of benign tumors invading veins, Aufrecht<sup>7</sup> in 1860 reported a case of primary myoma of the right saphenous vein originating in the region of the internal malleolus. The intima and adventitia of the vein were normal. Boettcher<sup>8</sup> in 1869 reported a case of a similar lesion in the ulnar vein except that all three coats of the vessel were involved. Schnijder<sup>9</sup> reported a case of myoma of the marginalis lateralis pedis. Cornil<sup>10</sup> in 1896 observed at autopsy

2. Ewing, J.: *Neoplastic Diseases*, ed. 3, Philadelphia, W. B. Saunders Company, 1928.

3. Ribbert, M. W.: *Geschwulstlehre für Aerzte und Studierende*, Bonn, F. Cohen, 1904, p. 258.

4. Bland-Sutton, J.: *Tumors Innocent and Malignant*, London, Cassell & Co., Ltd. 1917.

5. Borst, M.: *Die Lehre von den Geschwülsten*, Wiesbaden, J. F. Bergmann, 1902.

6. Nothnagel, C. W. H.: *Specielle Pathologie und Therapie*, Vienna, A. Holder, 1900, vol. 15, pt. 3, p. 540.

7. Aufrecht: Ein Myom der Vena Saphena, *Virchows Arch. f. path. Anat.* **44**:133, 1868.

8. Boettcher: Myom einer vena ulnaris, *Virchows Arch. f. path. Anat.* **47**:372, 1869.

9. Schnijder: *Centralbl. f. allg. Path. u. path. Anat.* **25**:529, 1914.

10. Cornil: Myomes dans les veines du bras, *Bull. Soc. anat. de Paris* **10**:725, 1896.

myomas with smooth fibers developed at the expense of the vascular walls of the veins of the arm. There was a myoma of the vena brachialis the size of a fist in which the muscular coat of the wall of the vein was completely involved. Cornil's report is only a short anatomic note on the autopsy.

Breus<sup>11</sup> reported a case of secondary myxoma of the vena cava ascendens and the heart. The original tumor was in the testicle whence the tumor cells spread through the plexus spermaticus. The venous tumor was not adherent to the vascular walls. Cernezz<sup>12</sup> also reported a case of myoma of the plexus spermaticus.

Cartilaginous benign tumors which invade blood vessels are not infrequent. Virchow,<sup>13</sup> in his work on tumors, included a report of an enchondroma originating in the fibula. There are some others reported in the literature, originating especially in the pelvic bones, as in the case of Pfeiffer.<sup>14</sup> These tumors generally degenerate into a malignant process; this will be referred to later.

I am unable to find a report of any other than the case of Langenbeck of a benign fibroid, but degeneration of the veins themselves occurs fairly frequently. As far back as 1860 Langenbeck<sup>15</sup> reported a case of a fibroid originating in the periosteum of the clavicle, which came to resection. The common jugular and also the subclavian vein were involved by extension of the tumor, and the internal jugular vein was thrombosed.

There are many cases reported in the literature of carcinoma forming primary, but more usually secondary, masses by direct extension within veins. In a recent issue of *The Journal of the American Medical Association*, Holt<sup>16</sup> reported the extension of a primary adenocarcinoma of the thyroid gland into the superior vena cava which was continued into the right auricular chamber and into the innominate, right subclavian, internal jugular and thyroid veins as well as downward into the inferior vena cava. Regarding malignant tumors, in this report I am, however, more directly concerned with sarcoma. Although dissemination of metastatic sarcoma by the venous route is common enough, actual vascular sarcomatous tumors within the veins by extension are rare. Sarcoma or more probably endothelioma may be a primary tumor.

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11. Breus: Ueber einem innerhalb des Venensystems bis in das Herz gewucherten Hodentumor, Wien. med. Wchnschr. 28:767, 1878.

12. Cernezz: München. med. Wchnschr. 58:676, 1904; cited by Van Ree.<sup>24</sup>

13. Virchow, R.: Virchows Arch. f. path. Anat. 8:404, 1855.

14. Pfeiffer, F.: Beitrag zur Lehre von dem Enchondrom des Beckens, Erlangen, F. Junge, 1890.

15. Langenbeck: Beiträge zur chirurgischen Pathologie der Venen, Arch. f. klin. Chir. 1:1, 1861.

16. Holt, W. L.: Extension of Malignant Tumor of Thyroid into Great Saphenous Vein and Right Heart, J. A. M. A. 102:1921 (June 9) 1934.

and Ribbert remarked that sarcoma of the vessels is usually primary and arises from the muscular wall, though not in all cases. According to Borst, an angiosarcoma may be of vascular origin, the tumor cells entering the vessel from without. Nothnagel, in his monumental work, referred to intravascular benign and malignant tumors.

Langenbeck<sup>15</sup> in 1861 reported a case of sarcoma which was primary in the parotid gland but which after several years extended to the internal jugular vein. In the same report he mentioned a case of sarcoma of the sheaths of the axillary vessels by extension from tissue in the vicinity of the pectoralis major and coracobrachialis muscles. He did not say if there were any masses of tumor cells within the lumens of the vessels.

Sarcoma of the wall of the aorta has been reported by Auffermann<sup>17</sup> and Miura.<sup>18</sup>

In Schrotter's<sup>19</sup> case a lymphosarcoma of the anterior mediastinal glands had ruptured into the vena jugularis and subclavian vein and the lumens of both veins were thrombosed. Similarly, in Lücke's<sup>20</sup> case a lymphosarcoma of the axillary glands ruptured through the wall of the left subclavian muscles and masses of cells were partly adherent to the wall of the vessel.

Perl<sup>21</sup> reported a case of primary sarcoma of the wall of the inferior vena cava, and Marrassini<sup>22</sup> one of a primary sarcoma of the deep jugular vein.

Razzaboni<sup>23</sup> more recently described a case in a man of 62. The condition apparently began in the lower limb without appreciable cause and was first considered phlebitis. The rapidly increasing tumor was preoperatively diagnosed as a sarcomatous tumor of the saphenous vein. There was recurrence within about a year after operation, followed by death. Histologic examination of the tumor revealed the absence of true elastic fibers and only some very fine fibrils. It was a connective tissue tumor of the sarcomatous type probably originating in the saphenous vein and arising from an old obliterating phlebitis of the saphenous vein of the thigh but without demonstrable metastases in the lymph

17. Auffermann: Primäre Aortengeschwülste mit eigentümlichen Riesenzellen, *Ztschr. f. Krebsforsch.* **11**:294, 1912.

18. Miura: Riesenzell Sarcoma der Aorta, *Festschr. f. R. Virchow*, Berlin, G. Reimer, 1891, p. 11.

19. Schrotter: Erkrankungen der Gefäße, in Nothnagel.<sup>6</sup>

20. Lücke, A.: Lymphosarcoma der Achseldrüsen, *Virchows Arch. f. path. Anat.* **35**:524, 1866.

21. Perl: Ein Fall von Sarcoma der Vena cava inferiore, *Virchows Arch. f. path. Anat.* **63**:378, 1871.

22. Marrassini, cited by Razzaboni.<sup>23</sup>

23. Razzaboni, G.: Sarcoma primitivo della vena safena interna, *Arch. ital. di chir.* **11**:483, 1920.

glands. There were a few giant cells. This, the author remarked, was not a tumor of endothelial or perithelional type, several of which have been described in the literature and some of which have been confused with true sarcoma. Van Ree<sup>24</sup> reported a somewhat similar case in a woman aged 42. There was a swelling in the medial third of the left tibia. She was operated on but died fifteen days later. At autopsy the thrombosed mass was removed from the great saphenous vein and was found to be microscopically sarcomatous. There were no metastases. This was a case of phlebosarcoma racemosum.

Ernst<sup>25</sup> at the autopsy of a girl 19 years old found a chondrosarcoma originating in the twelfth thoracic vertebra. The tumor had invaded the renal and suprarenal veins, the vena cava and the left ovarian vein, and there were masses of tumor tissue in the lumens of both pulmonary arteries. All these were extensions of the original tumor; there were no true metastases. Warren<sup>26</sup> found a mass, proved later to be a chondrosarcoma, palpable above the left sacro-iliac joint in a white man of 32 years. Autopsy revealed extensions into the common iliac, left femoral and left hypogastric veins and the inferior vena cava, and there were also metastases to the lungs. The author expressed the opinion that the tumor gained access to the venous system through the branches of the left hypogastric vein and from thence readily grew into the common iliac vein, extending from there. Here, as in my case, the intravascular masses lay for the most part free within the lumen of the vessel, being only slightly adherent. The cells were in the main well differentiated and produced a large amount of cartilaginous matrix.

Egdahl<sup>27</sup> in 1933 reported a case of primary intravascular tumor, probably a spindle cell sarcoma, somewhat similar to that in my case. The patient, a man, had always enjoyed good health, and there was no history of syphilis or gonorrhea. About nine years before Egdahl saw him a small nodule was noticed on the anterior surface of the right wrist near the midline which grew slowly and steadily until about two years before the time of the report it was the size of a golf ball. It grew rapidly and shot out a long tortuous branch with twigs which extended nearly to the elbow. There was no pain or inconvenience until shortly before the report was written, when the wrist began to ache and the forearm became reddish blue. The condition was judged

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24. Van Ree, A.: Phlebosarcoma racemosum, *Nederl. tijdschr. v. geneesk.* **1**: 759, 1919.

25. Ernst, P.: Ungewöhnliche Verbreitung einer Knorpelgeschwulst in der Blutbahn, *Beitr. z. path. Anat. u. z. allg. Path.* **28**:255, 1900.

26. Warren, S.: Chondrosarcoma with Intravascular Growth, *Am. J. Path.* **7**: 161 (March) 1931.

27. Egdahl, Anfin: Report of an Intravascular Sarcoma, *Tr. Chicago Path. Soc.* **11**:206, 1919.

to be malignant, and the tumor was removed. It shelled out easily, being covered with a glistening capsule. On examination it was found to be composed of veins filled with a firm, solid growth, but toward the tapering joints the growths easily slipped out of the veins like a finger out of a glove. The total length of the tumor was 29.5 cm., the main original portion being 7.5 cm.; the width at the widest portion was 4.5 cm. There were three radiating branches from the main tumor. The whole tumor was of firm, elastic consistency and of grayish color where cut. Microscopically, sections taken from all parts of the tumor showed as the predominant cell a spindle-shaped cell. The nucleus of the cell was fairly large, but mitotic figures were not numerous. In various places in the older part of the tumor degeneration was evident. The capsule covering the tumor and branches was found to show the histologic characteristics of a vein. On closer examination of the older part of the growth it was found that the tumor had apparently taken its origin from the wall of a blood vessel. The author was therefore led to believe that the tumor was an endothelioma but later, having had other opinions and made further examinations, he came to the conclusion that the most probable diagnosis was spindle cell sarcoma and that the site of origin was in the wall of the vein. Cells were found that could be called endothelial cells, but when two or more tissues are present in a tumor it is necessary to decide their relative importance. In Egdahl's case the spindle cells were entirely predominant in all parts of the main tumor and its branches. Much has been written in the literature on the subject of endothelioma and sarcoma, and cases of so-called endothelial growths in the veins have several times been reported, but Egdahl expressed the opinion that in practically no case has the origin of a tumor from endothelium been proved and that the continuity of a tumor with endothelium is not proof enough that it is an endothelioma. The histologic characteristics of the tumor in Egdahl's case favor the diagnosis of spindle cell sarcoma so strongly that the only possibility of its being an endothelioma would be on the assumption that the endothelial cells assumed the shape of spindle cells and appeared as fibroblastic elements, which they may at times do. But a study of the various sections would not warrant such an assumption.

In Egdahl's case there was no evidence of any invasion of a tumor from outside the vein. The growth was entirely intravascular. In my case the tissues surrounding the tumor were strongly invaded.

I am unable to find in the literature a report of any case of fibrosarcoma of the veins. It is possible that a sarcomatous tumor of the veins, either primary or secondary, may in time degenerate and thus become a fibrosarcoma, or the invading tumor tissue may already be a fibrosarcoma. However it may be, the pathologic and histologic evidence leaves no doubt that this tumor was a fibrosarcomatous invasion filling the lumen of the veins and that it was not an endothelioma.

## DISCUSSION

DR. R. W. McNEALY, Chicago: Dr. Davis has reported a case which is both unique and interesting. The usual mode of travel of metastases of sarcoma is by way of the veins. A sarcoma may arise from the walls of a vein, but authentic, carefully studied cases of this type are pathologic curiosities. In this case presented by Dr. Davis, as well as in similar cases, it seems to me that it is very difficult to be sure that the sarcomatous cells were offsprings of the mesothelial elements of veins rather than invading descendants of contiguous mesothelial tissues.

There has always been confusion in trying to separate the active rôle from the passive rôle which blood vessels play in tumors. The walls of vessels are made up of rather complex tissue, and true tumors of blood vessels are usually organoid. This does not mean, however, that individual histologic elements may not dominate to a degree which precludes a definite statement as to the tumor's exact origin.

In the case reported the tumor not only followed the course of the superficial veins but distended them in a remarkable sausage-like manner. The desmoplastic character of the tumor probably accounts for the preservation of the continuity of the strands of the tumor. Most tumor tissue is very friable and readily breaks off as emboli when a vessel is invaded.

Ewing called attention to the fact that tumors growing within vessels are permitted more freedom and often reveal their natural tendencies even more than the original tumor. One finds frequent references to intravascular growing tumors, and the distance that these tumors may extend from their sites of origin is in some cases almost unbelievable. Kellynack, in his book "Renal Growths," reported a round cell sarcoma in a boy 1½ years of age which had its origin in the kidney; the tumor broke into the renal vein and extended along it into the inferior vena cava, and thence as a thrombosis it projected into the right auricle. Instances of the extension of a tumor of the thyroid gland along the thyroid veins, jugular veins and superior vena cava into the auricle have been reported recently. Another common origin of extending intravascular growths is from tumors of the testicle. These tumors not infrequently invade the pampiniform plexus and follow the spermatic vein to the renal vein and even farther.

The histologic growth is interesting but does not offer the field for engaging speculation that is found in trying to explain the absence of demonstrable metastases in Dr. Davis' case. One can hardly conceive of this tumor growing to the extent that it did without millions of tumor cells having been cast adrift in the circulation. The low grade differentiation of the characteristic cells of this fibrosarcoma would lead one to believe that they would be very hardy and would probably survive in any except the most unfavorable environment. Undoubtedly the large majority of these vagrant tumor cells are destroyed in transit or after lodgment.

I have always been fascinated by the ability of some metastatic cells to grow in their new environment while others universally perish. In the present state of knowledge one is unable to offer any explanation of the fact that cancer of the breast gives rise to pulmonary metastases in a high percentage of cases while hepatoma, in which the growth early extends into the vessels, gives rise to pulmonary or other metastases very rarely.

It is remarkable that the patient in Dr. Davis' case still lives, and it will be interesting to follow him for a number of years to see if there is any recurrence of the tumor.



# CLINICAL AND HISTOLOGIC CHANGES PRODUCED IN CARCINOMA OF THE CERVIX BY DIFFERENT AMOUNTS OF ROENTGEN RADIATION

A COMPARISON

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If any marked advance is to be made in the use of current methods for the control of carcinoma of the cervix of the uterus, it will be necessary to deliver more adequate radiation to the parametrium. Radium applied to the cervix alone is capable of controlling disease within a distance of 3 or perhaps 4 cm. from the cervical canal in most patients without completely destroying normal tissues. This fact is illustrated by the relatively high percentage of cures among patients with early stages of cancer of the cervix. However, when the parametrium or the pelvic lymphatics are involved, some other means must be employed in an attempt to deliver a sufficient dose to these regions. Roentgen irradiation is the method most frequently used for this purpose.

The response of a malignant tumor to radiation is largely dependent on the dose delivered to the diseased area and the rate at which it is administered. A small dose delivered at high intensity over a short period of time may produce changes in a tumor that are comparable to those resulting from a larger dose delivered over a longer period of time. However, owing to the fact that tissues recuperate to a certain extent after exposure to radiation, a much greater dose can be tolerated when it is delivered by means of multiple small doses than when it is administered by single prolonged heavy exposures. Whether slowly administered radiation produces a greater effect than a rapidly delivered dose is uncertain. The factor of increased total dose must be considered when a protracted treatment with multiple small doses is employed. If the rate of recuperation of tumor tissue could be shown to be less than that of normal tissues, then there would seem to be a definite advantage in employing divided doses.

During the past few years an effort has been made at the Memorial Hospital to increase the dose delivered to the tumor-bearing regions located at a distance from the zone affected by radium applied to the

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From the Gynecological Service and Pathological Laboratories, Memorial Hospital, New York City.

cervix alone. This has been done by increasing the target skin distance for the roentgen treatment to raise the percentage depth dose delivered at each exposure. Furthermore, a protracted treatment with multiple small exposures has been employed to increase the total dose delivered to each area, keeping the skin reaction within the limits necessary to insure complete repair. Roentgen radiation has been delivered at various rates of administration and for different total doses.

Since 1929, radium treatment to the cervix has been preceded by a cycle of roentgen irradiation of the pelvis in all but the very early cases of cancer of the cervix. Therapy with divided doses was begun in 1933. By either means the patient can be given treatment without delay, and the application of radium at a later date can be accomplished with less trauma, and often with less technical difficulty, because of the regression in the size of the primary lesion following roentgen therapy. Moreover, bleeding and discharge from the cervix are lessened, and infection is diminished. Clinical observations and repeated biopsy on material from the cervix during the roentgen treatment afford information on the effect produced in the primary tumor by the roentgen rays, and hence it may be possible to glean some knowledge of the probable effect of similar doses on cancer of the parametrium, although one cannot assume that a tumor in a different anatomic location necessarily will be affected to a similar degree. Also, the response of a given tumor to a particular method of treatment may be observed histologically, even though the dose of roentgen rays is sublethal for most cancers of the cervix.

A total of forty-nine patients<sup>1</sup> have been studied by serial biopsies. All received roentgen treatment before the application of radium to the cervix. Roentgen radiation was delivered at different rates of administration, over various periods of time, for different total doses. In general, this group of patients was a fairly representative cross-section of all the patients with epidermoid cancer of the cervix seen in the gynecological clinic. All histologic grades were represented, although grades 1 and 3 formed an extremely small minority. In only two of the patients was there clinical evidence that the disease was still confined to the cervix. All of the others had parametrial involvement, and six patients had very advanced cases of the disease; thus they constituted a relatively hopeless group.

In order to compare the different degrees of regression noted in the various patients after roentgen treatment alone, it is necessary to consider the dose delivered to the cervix and the time required for the administration of this amount of radiation. The dose obtained in the cervix has been determined from data presented by Arneson and

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1. These patients were treated in the clinic of Dr. William Healy.

Quimby<sup>2</sup> and expressed in terms of threshold erythema doses. Under any circumstance the estimation of the tissue dose is only approximate. The dose delivered by roentgen irradiation was no doubt sublethal for cancer of the cervix in all but possibly one of the patients. Healy and Arneson<sup>3</sup> reported that the best results in the primary lesion were obtained when a minimum dose of 6 to 8 threshold erythema doses was distributed throughout its volume.

The roentgen treatment of a few patients consisted in delivering 700 roentgens in single exposures to each of four pelvic fields (two on the anterior surface and two on the posterior surface), each cutaneous field measuring about 15 cm. longitudinally and 10 cm. transversely. One treatment was given daily with an x-ray machine of 200 kilovolts at a target skin distance of 50 cm., with a filter of 0.5 mm. of copper and 2.5 mm. of aluminum. This method delivered about 0.85 threshold erythema dose to the cervix and adjacent parametrium over a period of four days. The cycle was repeated about six weeks after the radium treatment.

In 1933, a different method was adopted, in which the target skin distance was changed to 70 cm. Some of the patients included in the present series have been reported on in the previous description of this method.<sup>4</sup> Daily treatments of 200 roentgens were given to each of two pelvic fields. That is, the anterior and the posterior field on the left side would be treated on one day and the anterior and posterior field on the right side on the following day. This was continued until a total dose of 2,000 or 2,400 roentgens had been delivered to each area. The time of treatment required for the two total doses was three weeks and four weeks, respectively. The lesser amount of irradiation delivered about 2.5 threshold erythema doses to the cervix, and the greater amount delivered about 3.0 threshold erythema doses. The parametrium received somewhat less than the cervix.

In order to increase the rate of administration toward the end of the treatment, some patients were treated with five exposures of 200 roentgens followed by five exposures of 300 roentgens, making a total dose of 2,500 roentgens to each area. By this means about 3.1 threshold erythema doses were delivered to the primary lesion in a period of three weeks. Another group of patients were treated through six fields instead of four (two anterior, two posterior and one on each lateral surface) with daily exposures of 300 roentgens for a total dose

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2. Arneson, A. N., and Quimby, E. H.: The Distribution of Roentgen Radiation Within the Average Female Pelvis for Different Physical Factors of Irradiation, *Am. J. Roentgenol.*, to be published.

3. Healy, William P., and Arneson, A. N.: A Study of Carcinoma of the Cervical Stump, *Am. J. Obst. & Gynec.* 29:370, 1935.

4. Healy, William P., and Arneson, A. N.: Radiation Treatment of Carcinoma of the Uterine Cervix, *Am. J. Roentgenol.* 32:646, 1935.

of 2,100 roentgens to each area. In this method two opposite fields were irradiated each day, and the total time required for roentgen treatment was three weeks. About 3.2 threshold erythema doses were delivered to the cervix. The technic of using six fields has the advantage of delivering an even greater dose to the parametrium than to the cervix.

The radium treatment was the same for all of the patients. After the completion of the roentgen treatment an intravaginal applicator containing radon was placed against the cervix for a dose of 1,500 millicurie hours. On the following day a tandem consisting of two capsules (the lower one twice as strong as the upper one) was placed in the cervical and uterine canal for a dose of 3,000 millicurie hours. The filter in each instance was the equivalent of 2 mm. of brass. If a protracted treatment with multiple small exposures of roentgen rays was used, the patient was considered to have received complete irradiation after radium had been applied to the cervix, and no additional roentgen rays were administered. Further treatment was given only when the disease failed to disappear from the cervix or reappeared after a primary cure had been obtained. With a few patients it was necessary to apply radium to the cervix during the protracted roentgen treatment because the continued regression of the lesion and the contraction of the cervix threatened to increase markedly the technical difficulty of subsequent applications of radium. No detailed study has been made by biopsies after the treatment with radium, because complete destruction of the disease usually followed.

#### CLINICAL TYPE AND RESPONSE TO IRRADIATION

The patients presented a variety of different types of cervical lesions. Some were of an everting type of growth, cauliflower-like, usually soft, bulky, friable, vascular and sometimes ulcerated. Others were of an infiltrative type, usually hard, moderately bulky, sometimes nodular, frequently ulcerated and often infected. A few patients presented lesions which had completely destroyed the cervix, the latter having sloughed away, leaving an excavated, ulcerated, badly infected crater. The cauliflower-like and the infiltrative lesions seem to be distinct types. The cratered lesions, on the other hand, may have begun as either of the two varieties. As the disease progressed and the infection increased, the cervix sloughed away, leaving a crater. This explanation is substantiated by the fact that several of the patients gave a history of sudden hemorrhages, which may have marked the instant at which a large portion of the cervix was thrown off. One would therefore expect the cratered lesions to be more advanced than the other types. In general this was found to be true.

It is difficult to determine clinical criteria indicative of the response which a tumor may be expected to show under irradiation. The final

result after treatment is, of course, largely dependent on the stage of involvement to which the disease has progressed. However, there was a sufficiently marked difference in the response to treatment shown by the various types to warrant a discussion of these facts, despite the small number of patients in the series.

As was stated before, all of the patients received roentgen treatment before the application of radium to the cervix. They were observed carefully during the time that external irradiation was being given, and each patient has been examined at intervals ever since. The estimation of the degree of regression by clinical examination rests on individual interpretation, and results are consequently subject to error. Not only must the original condition of the diseased area be considered but the amount of radiation delivered to the tumor and the rate at which it was administered, when one attempts clinically to evaluate the response.

TABLE 1.—*Degree of Regression Noted in Primary Lesion After Roentgen Treatment Only and Present Condition of Patients After Complete Treatment According to Type of Lesion*

Type of Lesion	Number of Patients	Regression in Cervix from Roentgen Treatment Only			Present Condition after Roentgen and Radium Treatment		
		Good	Fair	Poor	Good	Fair	Poor
Cauliflower-like.....	23	19	4	0	17	4	2
Infiltrative.....	18	6	10	2	11	4	3
Cratered.....	8	1	3	4	2	1	5

Moreover, the patients have been treated too recently to make any definite statement as to the final result after treatment with radium. This is not important in the present study, since we are interested only in primary responses. However, it can be demonstrated that a greater percentage of the cauliflower-like lesions showed a good response to external irradiation and have remained in good condition up to the present time than of either the infiltrative or cratered types.

There were twenty-three patients (47 per cent of the group) who had cauliflower-like lesions. In nineteen of these patients the tumor showed good regression from roentgen treatment only, as manifested by shrinkage and contraction of the lesion. At the present time seventeen of these patients are in good condition following the completion of their treatment by the application of radium to the cervix. There were eighteen patients with infiltrative lesions, and in six the tumor showed good regression from roentgen rays. Eleven are now in good condition. Among the eight patients with cratered lesions, only one showed a good response to external irradiation, and only two are in good condition at the present time. These results are shown in table 1.

The poor results obtained in the group of patients with cratered lesions may be explained partially by the fact that these lesions usually

were more advanced than the other types. Infection and ulceration were also more marked in this group, and these factors sometimes complicated the course of the disease during treatment. The cauliflower-like lesions, on the other hand, presented a different situation. These lesions, more polypoid in form, did not infiltrate the fibrous stroma. They were more papillary in structure, and evidently they were nourished by a less stable blood supply. There were less infection and ulceration than in the other types. These factors probably contributed to the good response which most of these patients showed to treatment. However, this may not necessarily imply that a cauliflower-like lesion has a better eventual prognosis than other types.

Aside from the clinical evidence of regression, the changes produced in the different lesions can be studied also from repeated biopsies. Thirteen of the twenty-three cauliflower-like lesions showed marked changes, while nine of the infiltrative and three of the cratered types revealed a comparable alteration from roentgen irradiation. When expressed in percentages, the difference in the response to treatment, as shown by histologic study in the three types, was not as great as that observed clinically. This indicates that the clinical character of the lesion is more important in estimating the radiosensitivity of the local disease than are serial biopsies.

The total dose and the rate of administration of radiation also influence the degree and rapidity with which the tumor regresses. The patients have been grouped according to the method used for delivering roentgen rays, irrespective of the appearance of the primary lesion. There were nine patients who received 0.8 threshold erythema dose in the cervix over a period of four days, seven who received 2.5 threshold erythema doses in three weeks, thirteen who received 3 threshold erythema doses in four weeks, ten who received 3.1 threshold erythema doses in three weeks and ten who received 3.2 threshold erythema doses in three weeks.

Of the nine patients who received the smallest amount of roentgen radiation, in only one did the tumor show evidence of good histologic regression. Among the seven patients who received 2.5 threshold erythema doses in the cervix over a period of three weeks, in three the tumor showed good regression and of the thirteen who received 3 threshold erythema doses over a period of four weeks, in five the tumor showed good regression. In both of these last two groups about 40 per cent of the patients showed evidence of marked histologic changes from external irradiation. However, the patients who received a greater amount of radiation, that is, 3.1 and 3.2 threshold erythema doses, evidenced a greater percentage of marked changes in a shorter period of time (three weeks). These results are shown in table 2. Of the ten patients who received 3.1 threshold erythema doses in six (60

per cent) the tumor showed good histologic regression. In eight of the ten who received 3.2 threshold erythema doses (80 per cent), the tumor showed good histologic regression.

The patients in the group receiving 3.1 and 3.2 threshold erythema doses at the depth of the cervix within a period of three weeks developed the most marked cutaneous reactions. However, the damage to the skin remained within the limits of tolerance, and there was complete repair shortly after the treatment was finished. It is impossible to determine an optimum dose and rate of administration from the present knowledge of the recuperation of normal tissues and of tumor tissues. In the absence of such information and from the data obtained here on the regression of the primary lesion resulting from different methods of external irradiation, it would seem advisable to employ some form of protracted treatment delivering a large total dose at a fairly rapid rate of administration over a moderately short period of time.

TABLE 2.—*Histologic Changes Noted in Primary Lesion According to the Amount of Radiation Delivered to the Cervix by External Irradiation*

Dose Delivered to Cervix by Roentgen Irradiation Only	Number of Patients	Histologic Evidence of Regression		
		Good	Fair	Poor
0.8 threshold erythema doses in 4 days.....	9	1	2	6
2.5 threshold erythema doses in 3 weeks.....	7	3	1	3
3.0 threshold erythema doses in 4 weeks.....	13	5	6	2
3.1 threshold erythema doses in 3 weeks.....	10	6	3	1
3.2 threshold erythema doses in 3 weeks.....	10	8	1	1

#### CORRELATION OF THE DEGREE OF HISTOLOGIC CHANGES WITH THE CLINICAL REGRESSION NOTED IN THE CERVIX AND THE PRESENT CONDITION OF THE PATIENTS

As was stated previously, in each instance the primary lesion received a sublethal dose from external irradiation, with the possible exception of one. Moreover, the cervix was not destroyed in any patient by roentgen treatment. Because of the incomplete destruction of the cervix it is possible to correlate the histologic and clinical changes resulting from the roentgen rays. It has already been shown that varying percentages of marked histologic changes were obtained from different amounts of external irradiation. However, it is more difficult to correlate the histologic changes produced by the roentgen rays with the condition of the patients after the application of radium, because destruction of the cervix usually resulted thereafter, and the immediate results were more or less uniform. That is, the present condition of the patients who received 0.8 threshold erythema dose in the primary lesion from roentgen treatment is not markedly different from that of those who received 3.2 threshold erythema doses. The changes in the cervix were minimal in the group that received the smallest amount of

external irradiation, until after radium was applied. Because of the fact that most of the treatment delivered to the primary lesion in this group was with radium and because of the relative uniformity of the early results after the application of radium, these patients have been excluded from the comparison of the histologic changes with the clinical evidence of regression of the tumor from external irradiation and the present condition of the same patients. It may be expected, however, that a greater effect was produced in the parametrium beyond the radius of the action of radium applied to the cervix in the patients who received the greater amount of roentgen treatment.

Forty patients were treated with multiple exposures of roentgen radiation. In twenty-two of this number, the tumor showed evidence

TABLE 3.—*Degree of Regression Noted Clinically in the Cervix for the Patients with Tumors Showing Good, Fair and Poor Histologic Regression and the Present Condition of the Patients*

Histologic Regression in Patients Treated by Divided Doses of Roentgen Rays	Number of Patients	Regression in Cervix from Roentgen Treatment Only	Present Condition after Roentgen and Radium Treatment		
			Good	Fair	Poor
Good.....	22	Good (19 patients)	15	1	3
		Fair ( 3 patients)	3	0	0
Fair.....	11	Good ( 8 patients)	7	1	0
		Fair ( 3 patients)	2	0	1
Poor.....	7	Good ( 2 patients)	0	1	1
		Fair ( 2 patients)	0	0	2
		Poor ( 3 patients)	0	1	2

of good histologic regression. In eleven there were fairly good changes, and in seven the effect was poor. Among those who showed good changes, nineteen had good clinical regression of the tumor, and fifteen are now in good condition. Three showed only fair clinical changes but are now in good condition. Of the eleven who had fair histologic changes, eight showed a marked clinical response, of whom seven are now in good condition, and three showed a fair clinical change, of whom two are now in good condition. If the histologic change was poor (seven patients) a less marked change was noted clinically and the present condition is less satisfactory. These results are shown in table 3.

Since the correlation between clinical and histologic regression is imperfect, there must be some factors not ascertainable from biopsy which determine the degree of change from irradiation. If the treatment is adequate and the lesion is of the cauliflower-like type, the histologic changes are apt to be marked. If the histologic changes are marked, the clinical evidence of regression is usually good as well as the immediate results after complete treatment. Infection may play a part



in the response of the tumor, but the extent to which the disease has advanced is by far the most important factor.

#### PATHOLOGIC OBSERVATIONS

In a previous paper,<sup>5</sup> attention was called to the fact that little could be ascertained concerning the radiosensitivity of cervical carcinoma under methods of treatment then in vogue. It was believed that no significant quantitative data could be obtained concerning the radiosensitivity of the tumors when the therapeutic procedures employed involved the local application of quantities of radium directly to the lesion in doses which were certainly far beyond the lethal amount of radiation for a tumor near the applicator and far below that amount for a tumor situated at a few centimeters distant. Likewise it was considered probable that such data could be obtained, provided the tumors were treated with more uniform external irradiation of a type which would deliver more evenly distributed radiation throughout the tumor. Hence when the present clinical investigation was undertaken it was accompanied by the effort to determine, if possible, the differences in the response of histologically different epidermoid carcinomas.

Unfortunately, however, the patients available for this kind of treatment presented tumors very similar in histologic type. Practically all were rather typical plexiform epidermoid carcinomas (grade 2). Hence the group was unsuitable for determining differences, provided they exist, in the responses of different types. However, such decided differences appear to exist in the behavior toward radiation of comparable histologic types in different persons that we are forced to conclude that in a case of plexiform epidermoid carcinoma of the cervix a single biopsy is essentially useless for the estimation of the probable local clinical response to radiation. By local clinical response we mean that response to external irradiation alone given by the methods and in the doses described prior to the application of radium.

Apparently, as judged by our results, the response most to be desired from roentgen treatment with divided doses consists in what we prefer to call a progressive squamous degeneration. This term we employ to designate a series of changes characterized by swelling of the tumor cells, ballooning degeneration or pyknotic fragmentation of nuclei, a progressively increasing cytoplasmic opacity and acidophilia, a tendency to cornification, necrosis, leukocytic infiltration and slough, often followed by a foreign body giant cell reaction to necrotic squamous pearls and occasionally by calcification. The process seems to begin in a punctate fashion in single cells or in groups of two or three cells and rapidly spreads to involve the entire thickness of the individual

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5. Stewart, Fred W.: Radiosensitivity of Tumors, *Arch. Surg.* **27**:979 (Dec.) 1933.

sheets comprising the cancerous epithelium. In the relatively undifferentiated plexiform tumors, there is little evidence for believing that the process is a progressive degenerative differentiation from a basal layer of mother cells; the entire thickness of the carcinomatous epithelium seems equally involved. Figures 1 to 4 illustrate the process as observed in a single case by successive biopsies. It seems to us unnecessary to give once more the histologic description of this process. It is well known,

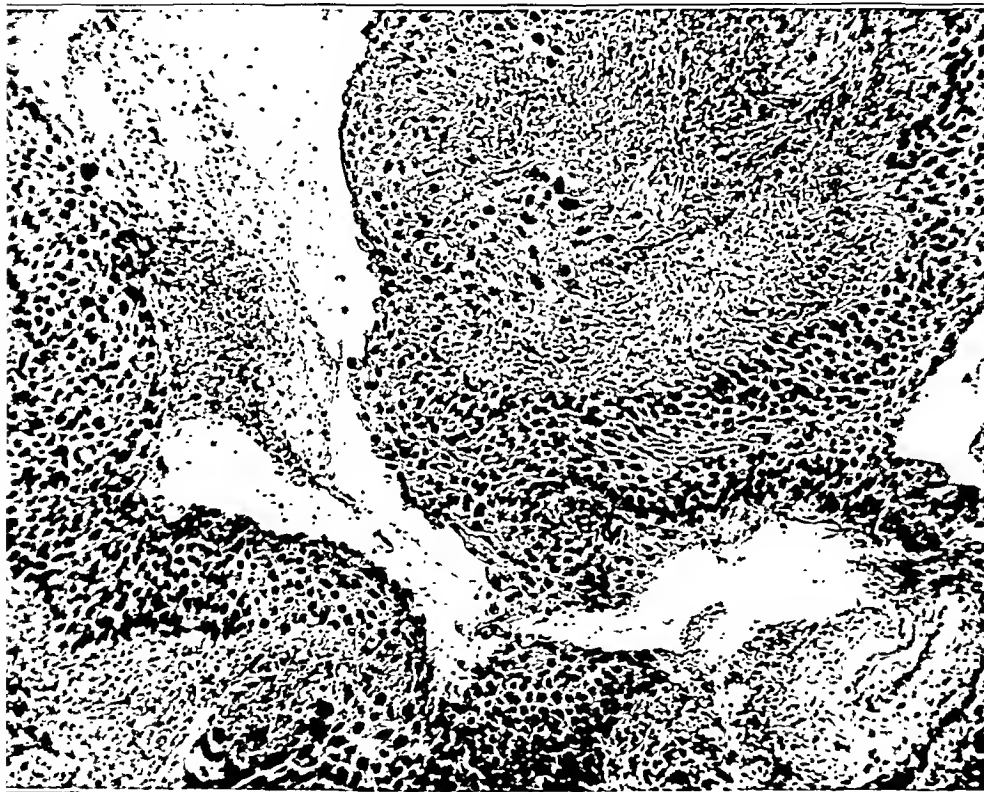


Fig. 1.—Plexiform epidermoid carcinoma of the cervix, grade 2.

particularly from the papers of Dustin<sup>6</sup> and the more recent work of Frola.<sup>7</sup> In rare cases in the present series this progressive squamous

6. Dustin, A. P.: Contribution à l'étude radiobiologique des épithéliomas du col utérin traités par la télécuriethérapie. Les courbes de pycnoses, de mitoses normales et de mitoses atypiques, *Bull. Acad. roy. de méd. de Belgique* 7:237 (March 26) 1927. Dustin, A. P.: Nouvelle contribution à l'étude radiologique des épithéliomas du col utérin soumis à la télécuriethérapie, *Arch. internat. de méd. expér.* 3:383, 1927.

7. Frola, Goffredo: Etude histologique et radiobiologique des tumeurs du col utérin traitées par la radiumthérapie, *Arch. internat. de méd. expér.* 8:289, 1933.

degeneration has proceeded to a point at which repeated biopsies showed no tumor and at which there was good reason to believe that a local cure had been obtained, although subsequent radium treatment was not omitted for this reason.

Unfortunately, however, the results of even serial biopsies are uncertain evidence of wholly favorable response on the part of the tumor. It is not infrequent after a series of biopsies in which the



Fig. 2.—The tumor shown in figure 1 after application of about 0.5 threshold erythema dose by external irradiation.

earlier specimens, obtained from shortly after the time the treatment began until doses of from 1 to 1.5 threshold erythema doses had been administered, showed a very favorable progress toward squamous degeneration, that the regressive phenomena cease and further biopsies show little or no alteration in the tumor. One is tempted to assume that observations of this sort must be considered evidence of radio-immunization of the tumor. In fact, on this basis a small series of patients was treated by progressively increasing doses in the belief that

an increase in the daily dose might overcome this radio-immunization and produce an orderly sequence of degenerative changes in the tumor which might not have occurred under constant daily doses. The patients who have been treated in this fashion are too few to permit any conclusion. We feel that it is desirable to treat a representative series of patients with cancer of the cervix in this fashion, but at the same time we must question the evidence on which the advisability of such methods of therapy has been suggested.

Material for biopsy is obtained from surfaces only of cervical carcinomas. Often the surfaces are ulcerated and infected. Spontaneous degeneration is common. It appears that radiation delivered to areas where there is a marked tendency to spontaneous degeneration and slough will often produce changes which will lead to an exaggerated notion of the effect in progress in less unstable portions of the tumor. It may well be that the appearances first interpreted by us as evidence of progressive radio-immunization are merely due to a chance selection of the specimen for biopsy; i. e., the material for the earlier biopsies was taken from superficial areas tending to spontaneous degeneration, and that for the later ones, showing little or no change, from deeper well nourished areas, as the tumor regressed and infection diminished.

This alternate explanation formulated, instead of one radio-immunization one finds support in two phenomena frequently observed in the course of serial biopsies. The first is the distribution of the effect of radiation in the tumors. Even in biopsies of small sections which rarely have a diameter exceeding 2 to 4 mm., it is readily observed that the changes due to the radiation may be very irregularly distributed. They may range from almost no alteration to nearly complete squamous degeneration. Such variations may be apparent within the range of a few microns. We have sought the explanation for these differences within narrow ranges in the irregular effects on the capillaries or in the irregularity of capillary distribution, but we have found no evidence for the direct support of this interpretation. When a tendency toward adult squamous differentiation exists in small foci of an otherwise relatively undifferentiated tumor, the maturation under radiation is most marked in those areas, and this may explain the focal character of the changes. This interpretation is quite consistent with observations on the effectiveness of roentgen therapy with divided doses on relatively differentiated, spontaneously maturing squamous carcinoma, repeatedly emphasized by the Paris school of radiologists. Hence it is probable that the condition is not radio-immunization in the sense that certain alterations take place to a given degree beyond which further radiation in similar doses fails to increase the degeneration, but that the areas which remain essentially unaltered by treatment represent portions of the tumor which with the doses employed for some reason escaped any

alteration. That such areas are not immune to larger doses appears from the fact that in most instances residua of the tumor after roentgen treatment responded in a normal fashion to radium.

Furthermore, we have observed repeatedly that even though serial biopsies show progressive degeneration of the tumor, nevertheless, if a delay of one to six weeks occurs between the date of the termination of roentgen treatment and the insertion of radium, a biopsy usually shows fully active carcinoma which in most instances cannot be distinguished



Fig. 3.—The tumor shown in figure 1 after application of a little less than 3.0 threshold erythema doses.

from the initial tumor. Since it is highly improbable that recurrences take place from portions of the tumor which have shown any decided advance in the direction of squamous degeneration, we are forced to conclude that parts of the primary lesion regularly escape degeneration with doses which are lethal or nearly lethal for other portions. Thus we have no justification for believing that the condition is radio-immunization or that the disease, influenced by constant daily doses up to a certain state of degeneration, would be influenced more markedly

by a process of pyramiding the daily dose, although we feel the desirability for more extensive experimentation with such methods.

Frola offered an interesting interpretation of these recurrences during the course of apparently satisfactory regression of a tumor due to irradiation. However, it is one which we cannot accept. Frola gave particular attention to the irradiated cervical mucous glands. He called attention to the bizarre appearances of these glands when areas or plaques of metaplastic epidermoid cells interrupt the columnar cell



Fig. 4.—The tumor shown in figure 1 after application of 3.2 threshold erythema doses. The lesion has disappeared except for a few degenerated squamous cells along the mid-border on the left.

layer. Apparently Frola is of the opinion that irradiation produces these metaplasias and that they may go on to the production of cancer. Hence he would see in the recurrences after irradiation a neogenesis of tumor at the expense of cervical mucous glands rendered metaplastic by the irradiation. He stated:

Tous ces phénomènes . . . s'observent vers la fin du traitement curiethérapique, après que plusieurs biopsies nous ont montré la disparition ou la nécrose avancée de la tumeur initiale. Les phénomènes si intéressants que nous avons pu

démontrer ne s'arrêtent pas ici. On peut parfois constater aux dépens des cellules mucipares métaplasées ou des cellules normales des glandes elles-mêmes, des phénomènes qui dépassent la simple métaplasie pour arriver à la véritable cancérisation. On assiste alors à la formation d'un véritable épithélioma spinocellulaire d'aspect morphologiquement semblable à celui de la néoplasie préexistante.

(All these phenomena are observed toward the end of the radium therapy, after many biopsies have shown us disappearance or advanced necrosis of the original tumor. The interesting phenomena which we have been able to show do not end here. One sometimes sees, at the expense of the metaplastic mucous cells or of the normal cells of the glands themselves, phenomena which go beyond simple metaplasia and into true cancer. One witnesses then the formation of a true spindle cell epithelioma with a morphologic picture like that of the pre-existent neoplasm.)

We believe that the evidence from our own series does not support Frola's contention but that certain of the phenomena observed may be the result of degeneration of areas of metaplasia caused by roentgen radiation, that others represent degenerative phenomena in persistent cancer lining the ducts of cervical mucous glands, and that there is no evidence for the assumption of neogenesis of tumor from such areas provided one uses the term to imply the formation of a new cancer under the influence of irradiation. Admitting the truth of Frola's statement that many cancers are the result of irradiation, it scarcely can be said that the factor of time which operates in the irradiation of cervical cancer is in any way comparable to those operative in the genesis of roentgen ray carcinoma. The majority of the histologic appearances observed by Frola represent undestroyed foci of cancer lining cervical glands. When the degenerative change is marked, there is no evidence that such foci regenerate active cancer. The regeneration proceeds from foci damaged to a much less degree, although there necessarily must be a point at which the balance between destruction of and capacity to regenerate local tumor is very delicate. The most interesting phenomenon in reference to the cervical glands is their ability to persist unaltered in the face of irradiation sufficient to destroy completely some carcinomas of the cervix. When recurrences of the carcinoma take place, their histologic picture usually entirely duplicates that of the original tumor. This would scarcely be so regularly the case if one were dealing with some such mechanism as Frola suggests. In our opinion they so closely resemble the original tumor merely because the original tumor was never destroyed, despite the evidence to the contrary from the normal results of one or more biopsies (figs. 5 to 7).

The initial biopsy, as we have previously intimated, offers no features which enable us to predict that under external irradiation the tumor will undergo an orderly progressive degeneration; nor does it, as a rule, offer an explanation for the failure for such evolution. However, serial biopsies occasionally show a series of events in the evolution of the



tissue under treatment which, even though they themselves lack explanation, may account for the failure of the tumor to show further satisfactory regression.

In a sense, these phenomena might well be considered a type of radio-immunization with alteration in structure toward histologic varieties usually considered as being more radioresistant tumors. The following case may be used as an example of this sort of change in structure.

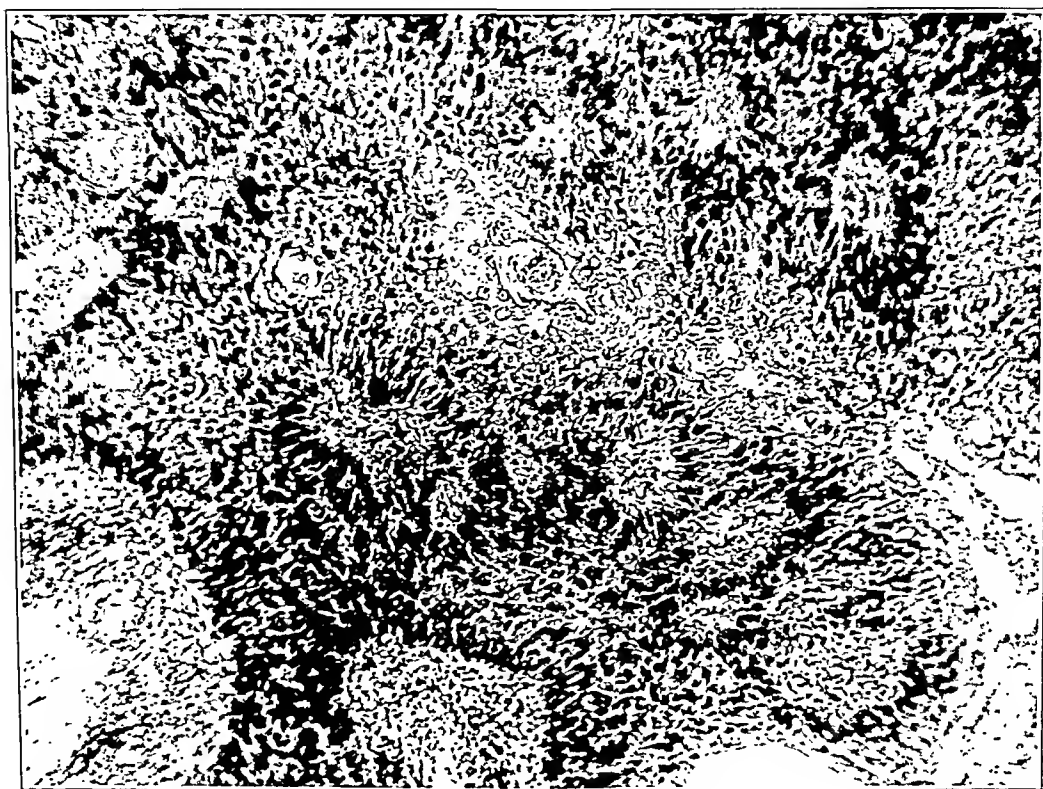


Fig. 5.—Plexiform epidermoid carcinoma, grade 2.

CASE 1.—M. B. presented a primary tumor, an advanced cauliflower-like lesion, 5 cm. in diameter, filling the vaginal vault and ulcerated. Histologic examination showed a diffuse anaplastic, small cell plexiform epidermoid carcinoma of grade 3. There was only a trace of spindle cell structure. The tumor was infected, and the interstices between the tumor cells were filled with polymorphonuclear leukocytes (fig. 8).

A biopsy made after 1 threshold erythema dose of roentgen rays had been applied showed the cells slightly larger, the cytoplasm pinkish and more opaque and plasma cells appearing in the exudate. After 2 threshold erythema doses, there was fairly marked squamous degeneration. The cells were large and loose and



appeared not unlike decidua. An increased tendency toward spindle cell change was noted, and atypical tumor giant cells appeared. After the application of 2.5 threshold erythema doses, the cytoplasmic opacity had increased still further, and the spindle cell structure was very decided (fig. 9). A biopsy after 3 threshold erythema doses had been given showed a less marked stage of alteration; a second examination showed slough only, but a third showed the tumor to be made up of atypical polyhedral spindle and squamous cells lying in the midst of thick hyaline tissue (fig. 10), probably a product of the degenerating tumor. A biopsy of a section secured two weeks later showed, in addition to this spindle cell structure,

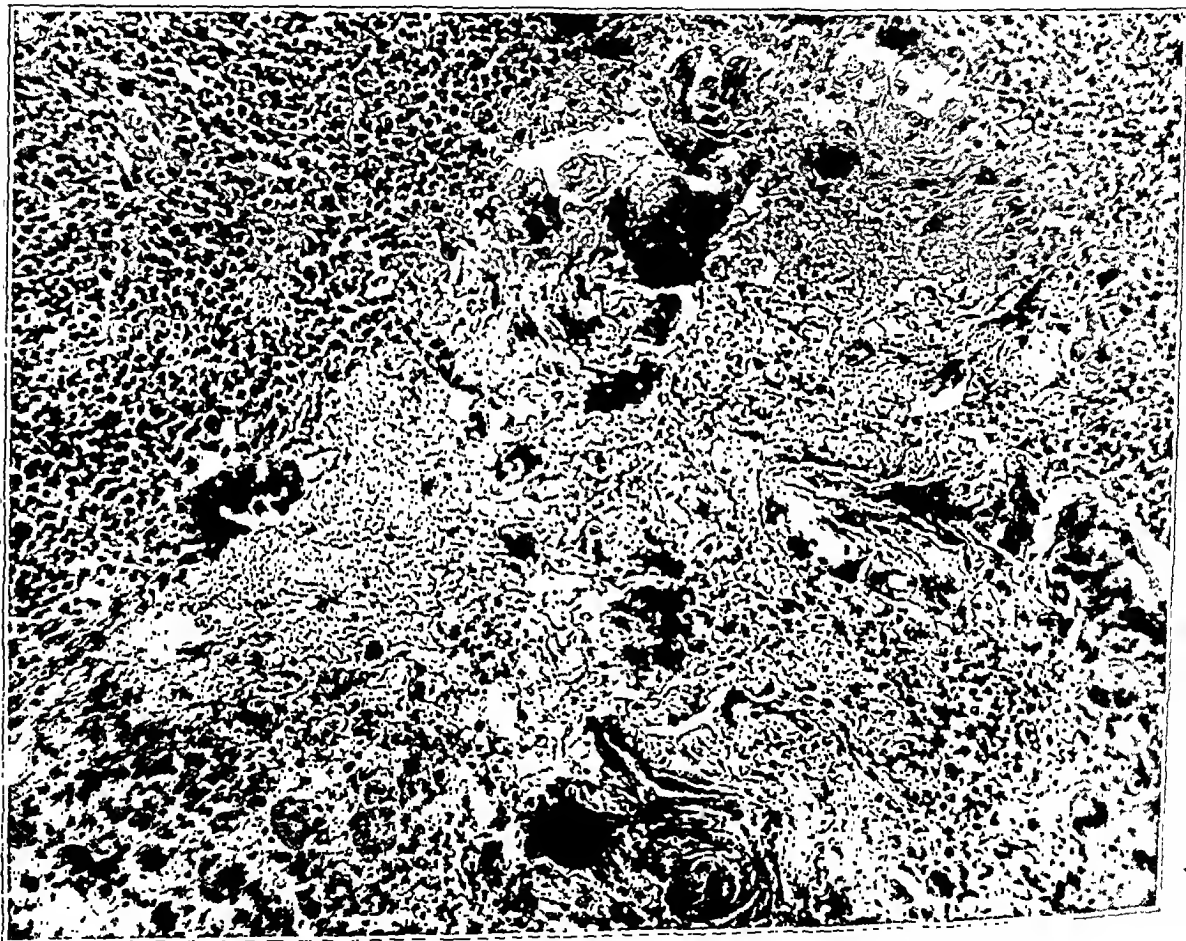


Fig. 6.—The tumor shown in figure 5 after application of about 3 threshold erythema doses. The biopsy shows only masses of degenerated sloughing squamous cells.

a small area of fully active cancer and a focus resembling low grade adult squamous carcinoma (fig. 11). Furthermore, even after application of radium for a dose estimated at about 10 threshold erythema doses additional to the site from which the biopsy specimen was taken, disease persisted in the cervix, finally resembling in structure the original tumor.

In two other cases successive biopsies showed areas of tumor, in one instance resembling adult squamous carcinoma and in the other scarcely more than adult papilloma. It is open to question whether in

these three cases we observed regressive changes in what were originally homogeneous anaplastic or plexiform carcinomas leading to the development of adult forms or whether we were dealing with mixtures of types from the beginning. On the one hand, pathologists who are familiar with the changes produced by irradiation in tumors are well acquainted with the phenomenon of physiologic maturation as part of regression due to irradiation. On the other hand, it is quite possible

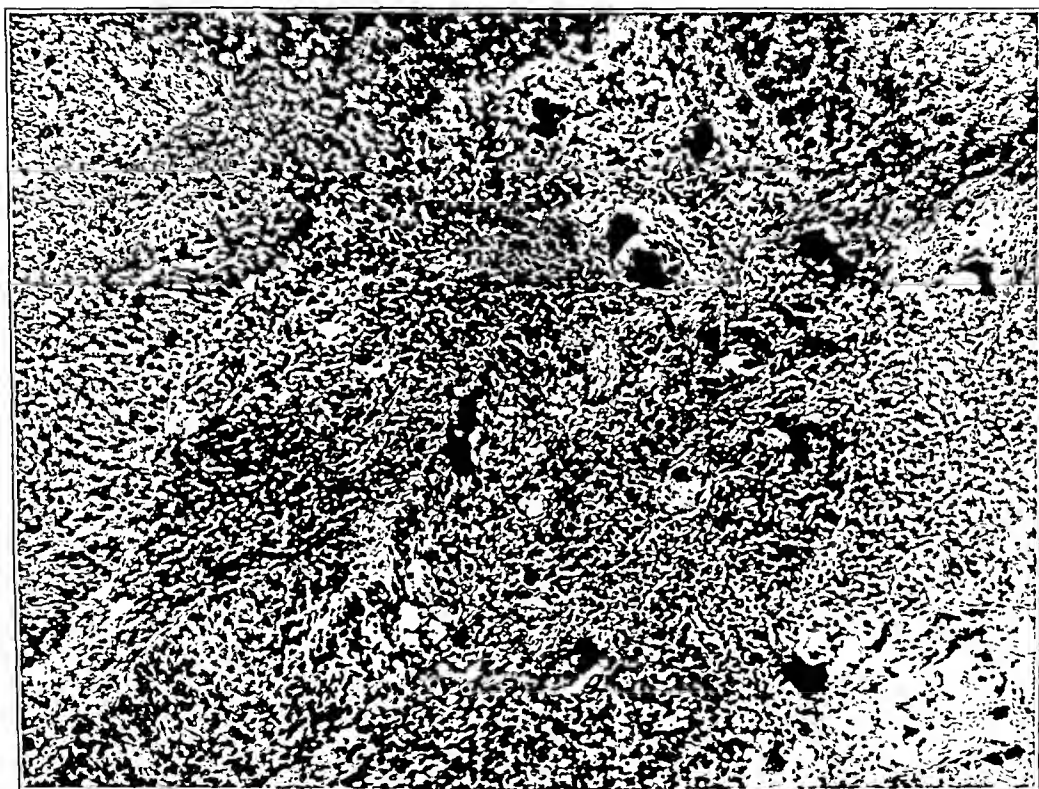


Fig. 7.—The tumor shown in figure 5 four weeks after application of 3 threshold erythema doses. Residual degenerated calcified squamous cells are surrounded by fully viable tumor, not distinguishable from the original tumor.

that the structure of the original lesion was complex. From the study of the biopsies we are inclined to interpret the spindle cell metaplasia with hyaline degeneration as the result of irradiation, and we are inclined to doubt the development of fully adult forms of the carcinoma following irradiation, although it may be that in areas where the tendency to form adult cells was marked in the original tumor there was an accentuation of the process under irradiation. That irradiation may produce a peculiar spindle cell metaplasia accompanied with very

marked radioresistance almost amounting to an absolute insusceptibility to radium has been known in the case of certain carcinomas developing on the basis of chronic roentgen ray dermatitis. In cervical cancers in which these phenomena were encountered, the appearances were only temporary. Hence it is unlikely that the failure to respond to treatment was more than temporarily influenced by the alteration in structure, since successive biopsies showed a return to the original structure.

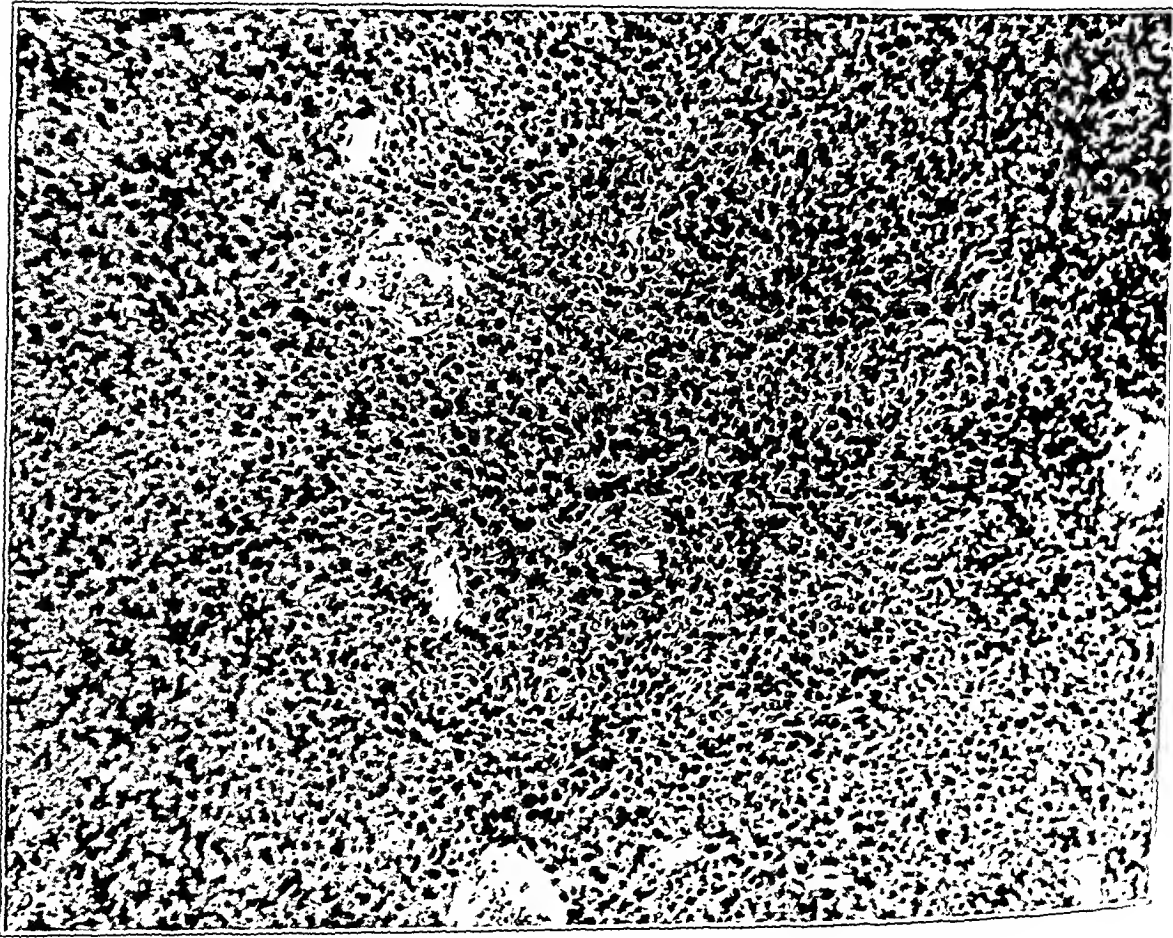


Fig. 8.—Anaplastic diffuse epidermoid carcinoma, grade 3.

Material is insufficient to determine whether any particular type of cervical carcinoma tends to undergo spindle cell metaplasia under irradiation. As a rule, we perform only a single biopsy prior to treatment. That is insufficient to give any idea of what structural varieties may be present in different areas of the tumor. The possibility suggested itself to us that spindle cell metaplasia might be expected to occur in cases in which in the original tumor there was a tendency to perilobular keratinization, as in tumors of the type described by Regaud and

Gricouroff<sup>8</sup> as *épithélioma épidermoïde à kératinisation périlobulaire* or as *épithélioma pavimenteux stratifié, à évolution épidermoïde, à transformation cornée péricordone*. This would be in line with Krompecher's<sup>9</sup> description of spindle cell carcinomas originating in an elongation of the basal cell. We have been unable to support this thesis. It does appear to be a fact that spindle cell metaplasia is most often associated with the fungating cauliflower-like type of tumor.

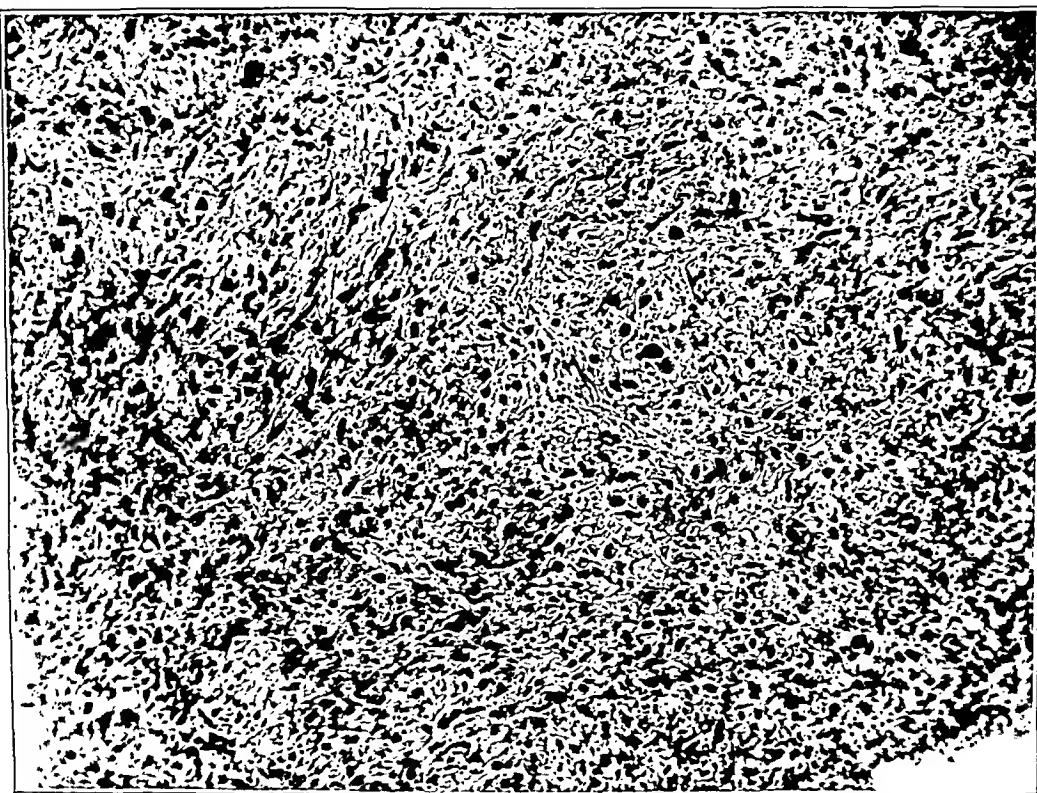


Fig. 9.—The tumor shown in figure 8 after application of about 2 threshold erythema doses. Spindle cell metaplasia is present.

Spindle cell areas alone do not appear to be a criterion for determining increased radioresistance. We emphasized spindle cell metaplasia accompanied by a peculiar hyaline production which is probably a stage of beginning abortive fibrosis. We feel that variations in the resistance in these relatively undifferentiated types of cervical carcinoma

8. Regaud, C., and Gricouroff, G.: *L'épithélioma épidermoïde du col de l'utérus à kératinisation périlobulaire*, Ann. Surg. **93**:360, 1931.

9. Krompecher, E.: *Der drüsenartige Oberflächenepithelialkrebs: Carcinoma epitheliale adenoides*, Beitr. z. path. Anat. u. z. allg. Path. **28**:1, 1900.

for the most part must lie in features of the tumor not ascertainable from superficial biopsy. The most marked resistance noted in this series seemed to be that of a patient with a positive Wassermann reaction. This agrees with the observations on the radioresistance of lingual carcinoma associated with syphilitic glossitis. The most sensitive tumor occurred in a patient who was pregnant. Biopsy failed to show significant differences in the types of tumor in these two patients.

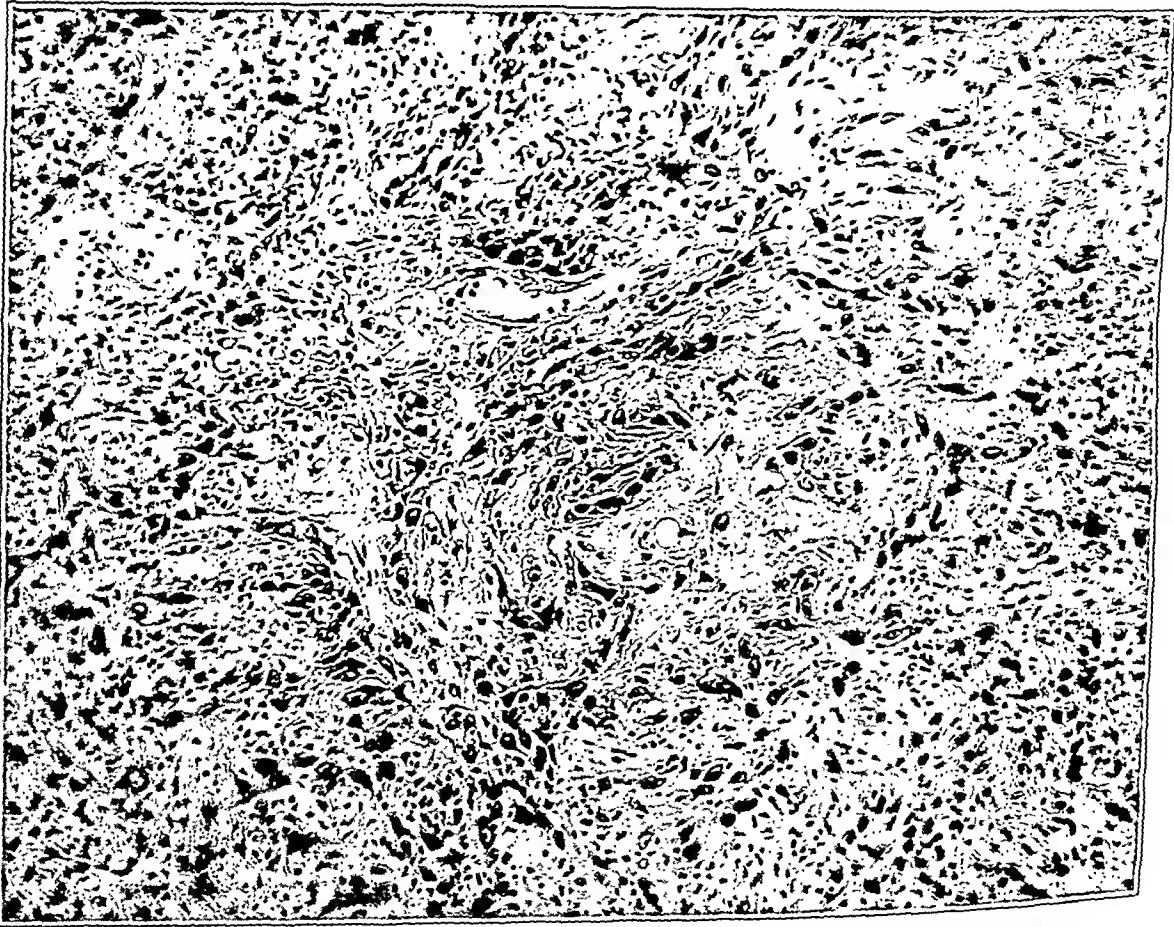


Fig. 10.—The tumor shown in figure 8 after about 3 threshold erythema doses. Spindle cell metaplasia, hyaline degeneration and beginning abortive fibrosis are seen.

As is readily seen from the tables, in the majority of patients treated with divided doses there was very decided regression of tumors from external irradiation alone, and there was a definite tendency in most cases for the clinical regression to parallel the histologic evidence of alteration. However, in a few cases the phenomena diverged. In such cases the clinical result appeared more impressive than the histologic result. It may be well to cite a case in point.



CASE 2.—B. C. presented an advanced, ulcerated, cauliflower-like lesion filling the vaginal vault. Histologic examination showed a typical plexiform epidermoid carcinoma. The blood supply, so far as could be ascertained from biopsy, was delicate. Lymphoid stroma was present. There was a polymorphonuclear exudate over the ulcerated surface. After 0.5 threshold erythema dose of roentgen rays the lymphoid infiltration was more marked. The cells became somewhat larger and more opaque. The mitoses averaged one per field (high power). The changes in general were slight. After 1 threshold erythema dose, slight squamous degenera-

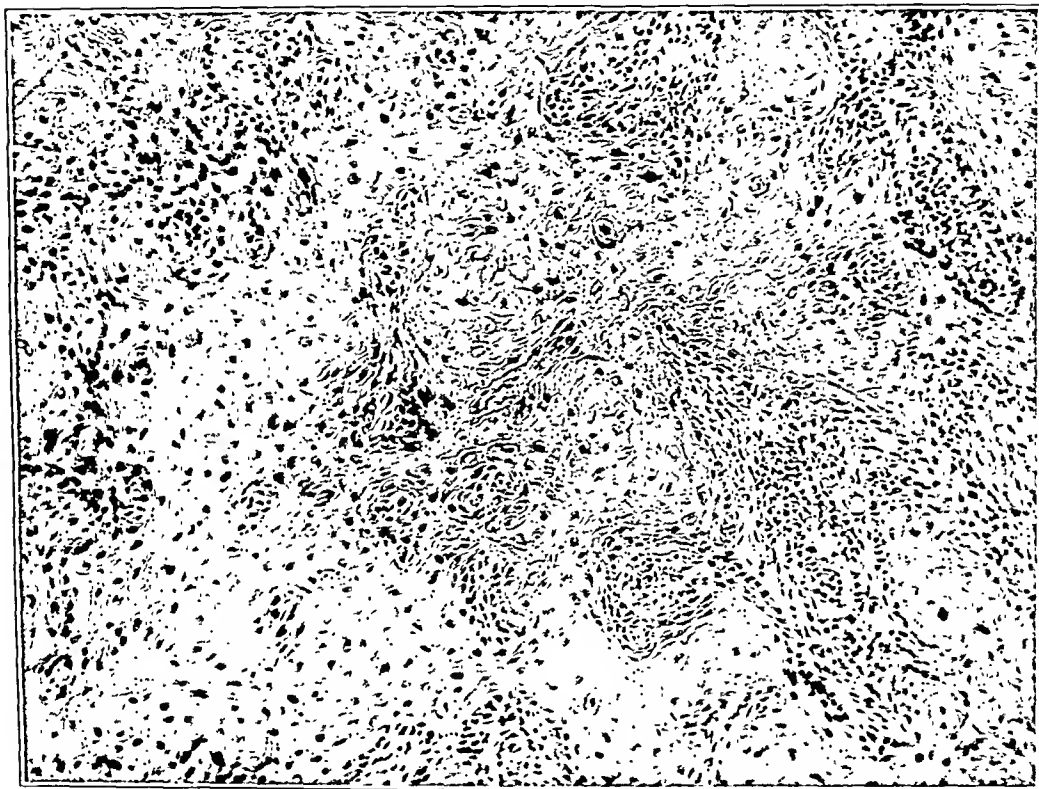


Fig. 11.—The tumor shown in figure 8 three weeks after application of about 3 threshold erythema doses. It is now an adult squamous cancer.

tion occurred. Degenerative giant cells were present. There was a slight tendency to spindle cell metaplasia and no reduction in mitoses. After 1.5 threshold erythema doses, there were decided differences in various portions of even a small section taken for biopsy. Some areas showed moderately advanced squamous degeneration. Others showed no changes from the original status. After 1.5 threshold erythema doses (second biopsy) there was little change; many plasma cells appeared and the spindle cell areas were more marked. After 2.5 threshold erythema doses there was no change. After 3 threshold erythema doses the tumor was essentially unaltered. Twelve days and seventeen days after 3 threshold erythema doses the tumor was unaltered.

Despite the unsatisfactory character of the histologic change during treatment, the clinical result was described as "good regression from roentgen treatment; cervix completely healed after treatment with radium but hard and nodular." Six months after radium treatment a membrane developed over the cervix, hemorrhage occurred, and a rectovaginal fistula developed, but no evidence of disease could be found. It is difficult to understand how a tumor can regress well clinically and

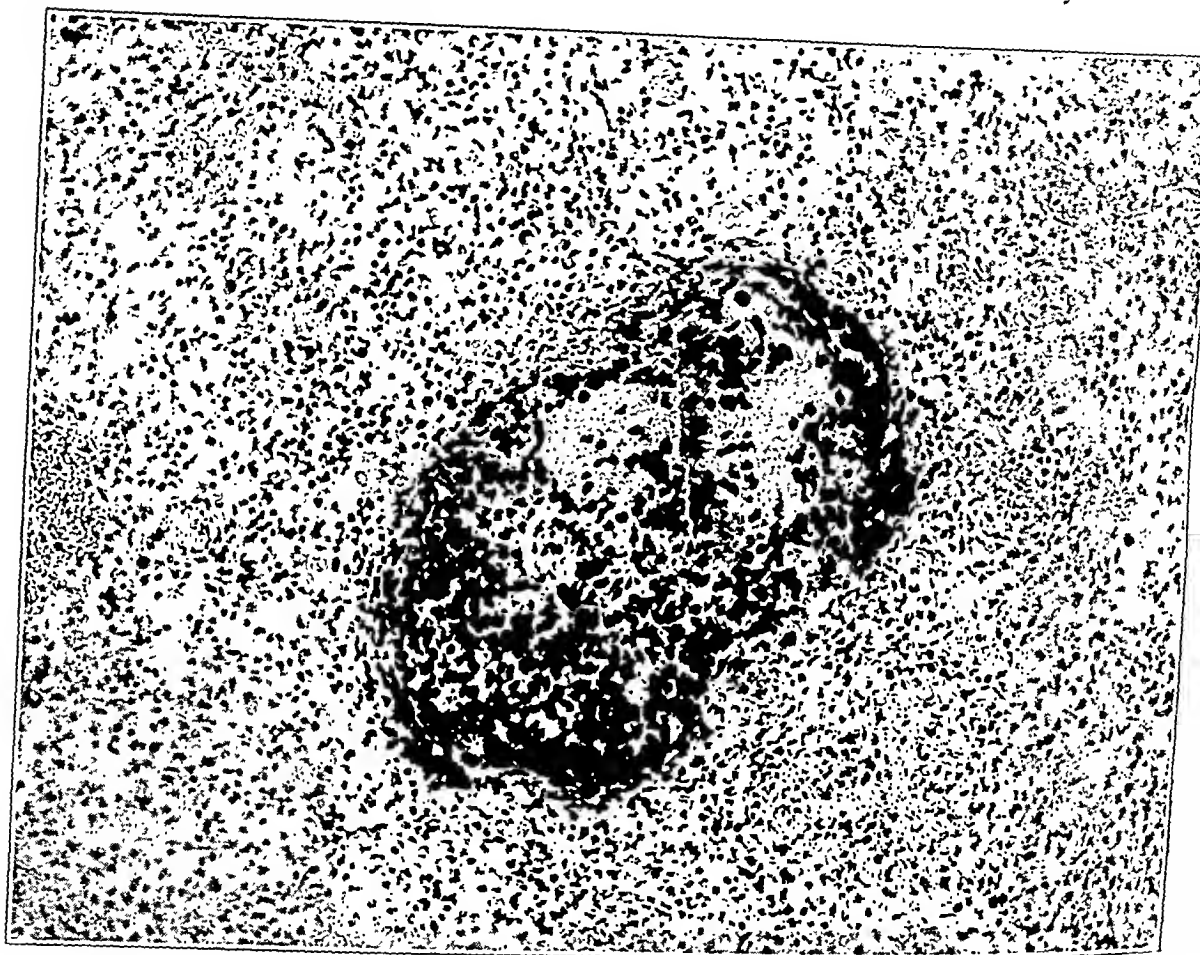


Fig. 12.—Anaplastic epidermoid carcinoma, showing degeneration in the midst of acute exudative inflammation and isolated clusters of naked hyperchromatic nuclei in the midst of degenerative hyaline tissue.

yet retain a histologic character closely resembling its original appearance. Diminution in infection is scarcely sufficient to explain the phenomenon, and we are inclined to interpret it as a result of the chance selection of the material for biopsy, or the selection of material from the most unaltered part of the lesion for section. Suffice it to say that repeated biopsies indicating no essential histologic changes in the structure of a tumor during treatment may not necessarily mean that no clinical reduction is occurring.

We have dealt up to the present time with the histologic features involved in the regression of the typical plexiform epidermoid carcinoma of the cervix (called basal cell carcinoma or transitional cell cancer in certain clinics). As we stated, during the time of the present investigation our material consisted almost entirely of such types. Hence we have little information on the processes of regression of certain very anaplastic carcinomas. The type of regression of these varieties is probably not uniform. We found one tumor radioresistant and undergoing spindle cell metaplasia with hyaline degeneration and beginning abortive fibrosis. Another, however, seemed to disappear by breaking up into small clusters of almost hyperchromatic naked nuclei in the midst of degenerative hyaline material, accompanied by an acute exudative inflammation (fig. 12). Whether or not this is a common type of change due to radiation in tumors of this variety cannot be stated without much more evidence. The material taken for biopsy included a very small number of tumors probably originating in and duplicating in an abortive fashion the ducts of cervical glands (pseudoglandular types). It was thought that these might prove more radioresistant, but this has not proved to be the case.

#### COMMENT

At the beginning of this paper mention was made of the necessity of increasing the dose of the roentgen rays to the parametrium if any marked improvement was to be made in the cure of cervical cancer. The clinical and pathologic changes following different amounts of external radiation delivered to the primary tumors of the cervix were studied in the hope that they might prove an index to what was going on in the parametrial extensions. Two facts seem definite. First, the quantity of external radiation introduced into the primary tumor by the methods so far employed will not cure more than a very small percentage of cervical carcinomas. Hence we are forced to the conclusion that by such methods cure of parametrial disease of established character will be equally rare. Second, it is unlikely that doses to the parametrium of the order considered in this paper will lead to any marked degree of restraint in growth in the average case, since observations on primary tumors indicate that after nonlethal doses of roentgen rays recurrence of the tumor in its original histologic form is rapid.

On the other hand, there is both histologic and clinical evidence of very marked regression of these primary lesions, and the necessary conclusion must be that different parts of the primary lesion undergo regression under different quantities of radiation even though the fundamental histologic structure is relatively similar throughout. There is a very decided difference in the order of the dose which will produce marked regression clinically and that which will produce complete histo-



logic sterilization. Since histologic observations indicate that differences in the extent of destruction of the tumor may exist even in very small areas it may be possible that in the exceptional instances of early stages of parametrial cancer, the recent unestablished nodular embolus, a dose of the order possible by the present method of external irradiation with divided doses will result in a cure, but such a favorable series of circumstances would be a rarity. Cure of an established parametrial extension of the average cervical cancer cannot be anticipated with external irradiation in the amount heretofore given. It may possibly cure exceptional, highly sensitive tumors.

The question arises whether under such circumstances it is worth while to pursue a protracted course of external irradiation. We are of the opinion that it is, not because it will result in a decided increase in the curability of the average cervical cancer but because it may be a factor of decisive importance in an occasional case. There is a large gap between the 3.2 threshold erythema doses delivered by the present method and the 6 to 8 threshold erythema doses which we found most effective in radium treatment of the average primary cervical cancer. It is very possible to close this gap partially if one is willing to accept a greater degree of initial cutaneous reaction and rectal and vesical irritation as the dose delivered by external irradiation is increased. Although this may be unwarranted in favorable early cases, it seems well warranted in borderline and advanced clinical cases in which conservative methods have little to offer the patient.

#### SUMMARY AND CONCLUSIONS

Attention is called to the necessity of delivering a larger dose of external radiation to the parametrium if any advance is to be made in the cure of cervical carcinoma.

An attempt in this direction is described. The treatment consists in increasing the target skin distance for external irradiation from 50 to 70 cm., using multiple portals (from four to six) and delivering at least 2,000 roentgens to each field within a period of about three weeks.

This method delivers approximately from 3 to 3.2 threshold erythema doses to the cervix and somewhat less to the parametrium if four portals are used and slightly more if six portals are employed.

Serial biopsies have been studied throughout the course of treatment by roentgen irradiation. The histologic process of regression has been followed, and comparisons have been made between the histologic changes and the degree of clinical regression.

The percentage of satisfactory clinical regressions parallels the increase in the doses. The histologic regressions tend to parallel the clinical regressions. Exceptions are noted.

The lesions are classified into groups based on their gross anatomic character. Polypoid lesions show the greatest clinical regression with external irradiation. Crateriform lesions appear the least susceptible. The latter usually constitute a more advanced clinical type of disease.

Local cure from external irradiation is exceptional with the doses used. By cure is meant complete anatomic disappearance of disease as evidenced by repeated normal results from biopsies over a period of time. One or two normal results are not evidence of cure. Complete temporary epithelization of the primary lesion is not uncommon.

Despite successive biopsies showing progressive degeneration of the tumor and occasionally complete disappearance of disease in one or more specimens examined at the end of the period of external irradiation, the tumor tends almost inevitably to reappear in a histologic form which is apt to resemble closely the initial tumor. Hence restraint of growth is but a transient phenomenon.

For this reason we have little hope that the methods described will control more than a minor percentage of tumors with parametrial extensions. There is a wide gap between the dose delivered to the parametrium by roentgen irradiation (about 3.2 threshold erythema doses) and the 6 to 8 threshold erythema doses necessary for the cure of primary cervical cancer in its usual form. It is thought, however, that the dose to the parametrium may be increased somewhat.

# LONGITUDINAL GROWTH OF LONG BONES

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AND

M. E. BISGARD, B.A.

OMAHA

Knowledge of the growth of long bones had its beginning with the observations of Stephen Hales<sup>1</sup> in 1747. He drilled two holes in the shaft of the tibia of a growing chicken, and when he examined the bone two months later he found that although the shaft had increased 1 inch in length, the distance between the two holes had remained the same. He also observed that most of this length had been gained at the proximal end. He concluded that growth in the length of long bones is accomplished entirely by deposition of new bone at the extremities and that the amount of growth from the two ends is unequal. These observations have been confirmed by similar experiments of many investigators, among them Hunter,<sup>2</sup> Duhamel,<sup>3</sup> Ollier,<sup>4</sup> Wegner,<sup>5</sup> Humphry,<sup>6</sup> Payton,<sup>7</sup> Kölliker,<sup>8</sup> Haas<sup>9</sup> and Gatewood and Mullen.<sup>10</sup>

Clinical evidence of unequal growth from the two ends of long bones was noted first by Ollier.<sup>4</sup> He observed that children matured with great shortening of a leg in which the knee joint had been resected

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From the Department of Clinical Research, University of Nebraska, School of Medicine.

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9. Haas, S. L.: *Interstitial Growth in Growing Long Bones*, *Arch. Surg.* **12**:887 (April) 1926.

10. Gatewood and Mullen, B. P.: *Experimental Observation on the Growth of Long Bones*, *Arch. Surg.* **15**:215 (Sept.) 1927.

but with only slight shortening of an arm in which the elbow joint had been removed. He calculated that two thirds of the growth of the leg takes place from the ends of the bones which form the knee joint (the distal end of the femur and the proximal ends of the tibia and fibula) whereas in the arm, only one fifth of the growth occurs at the ends which form the elbow joint.

The first complete and definitive measurements of the quantity of growth which takes place from each end of each principal long bone appeared in 1915. Digby<sup>11</sup> ingeniously reasoned that the nutrient vessels around which long bones begin their formation maintain their original positions at the center of the medullary canals as growth progresses. Thus by projecting the nutrient canal (which always traverses the bone obliquely) until it intersects the center of the medullary canal, the point from which growth started is determined, and growth from each end is measured from this point.

To determine the accuracy of this method of measuring growth and to obtain actual measurements of growth from each end of the principal long bones, the experimental studies herein recorded were carried out.

#### EXPERIMENTS

New-born goats were used for the experiments so that records of the entire postnatal period of growth could be obtained. Goats were used because they are hardy and survive extensive operations performed during the first few days of life and because they have a substantially large range of growth.

To measure growth the bones were marked with steel shots placed in drill holes in the shafts when the animals were from 2 to 5 days old. All operations were performed with rigid aseptic technic and with the animal under ether anesthesia.

Roentgenograms were taken of the bones at the beginning, throughout the course and at the end of the experiments, which extended over the period of major growth (from twelve to eighteen months). All examinations were made with the extremities in direct contact with the films and with a precisely constant technic.

Final measurements from which growth calculations were made were obtained by actual measurement of postmortem specimens.

##### EXPERIMENT 1.—*No Interstitial Growth.*

Since the animals used in this study were new-born and were therefore much younger than those used by Wegner,<sup>5</sup> by Gatewood and Mullen<sup>10</sup> and by others, it seemed necessary to repeat their experiments to preclude the possibility of interstitial longitudinal growth of the shaft during early postnatal life.

In twin goats 4 days old shots were placed at measured distances along the entire shaft of a long bone, the humerus in one animal and the radius in the other. Roentgenograms of these bones taken at monthly intervals for the first five months and at postmortem examination twelve months after operation showed that the distances between the shots had constantly remained unchanged. In the postmortem specimens the shots were exposed by grinding away the bone which had been deposited over them, and from actual measurements it was found that the shots

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11. Digby, K. H.: The Measurement of Diaphyseal Growth in Proximal and Distal Directions, *J. Anat. & Physiol.* 50:187, 1915.

were the same distances apart as when originally placed, thus confirming the observations of the investigators referred to previously. Normally all postnatal longitudinal growth of long bones is accomplished by the addition of new bone at the diaphyseal extremities; there is no interstitial growth in length (fig. 1).

EXPERIMENT 2.—*Measurements of Longitudinal Growth.*

To determine by actual measurements the proportion of growth which takes place at each end of each principal long bone, shots were placed at a measured distance (from 2 to 6 mm.) from the epiphyseal cartilages at each end of the shaft in goats from 2 to 5 days old. Roentgenographic records were made monthly for

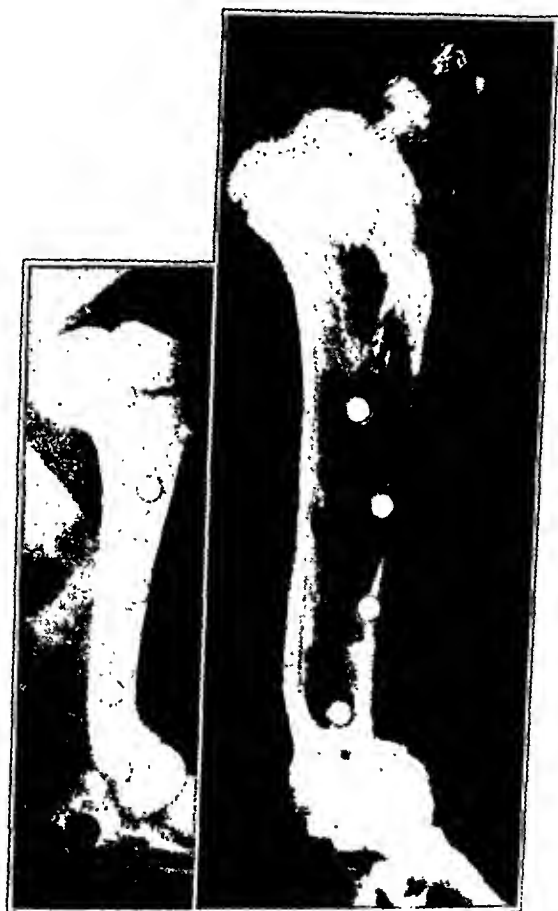


Fig. 1.—Right humerus of a goat at the ages of 4 and 358 days. Shots which were placed in the shaft at measured intervals remained equidistant as the bone lengthened. All growth occurred at the ends, principally the proximal end.

five months and then bimonthly until the animals were killed, from sixteen to eighteen months after operation. Representative serial records are reproduced in figure 2. In the postmortem specimens the shots were exposed and exact measurements were made of the distance between the shot and the end of the diaphysis at each end. The difference between these measurements and those recorded at the beginning of the experiment represents the distance that the epiphyseal lines had moved during growth away from the shots, which remained as fixed points to mark the original location of the epiphyseal lines.

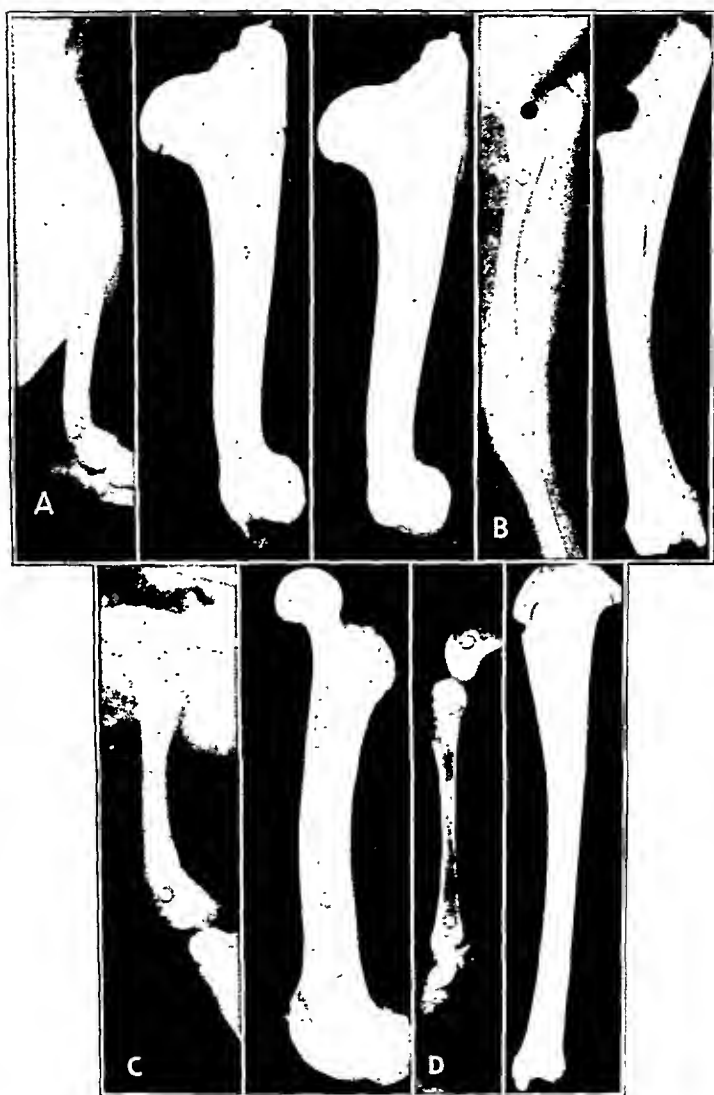


Fig. 2.—A record of postnatal longitudinal growth from the ends of each principal long bone of goats. The ends of the diaphyses were marked with shots placed in drill holes in the cortex when animals were new-born. *A* shows the growth of the right humerus from the age of 2 to 480 days. Both humeri at maturity are pictured to show that they are equal in length and that operative interference in the right one did not disturb normal growth. *B* shows the growth of the right radius at the ages of 4 and 468 days; *C*, of the right femur at the ages of 2 and 480 days; *D*, of the right tibia at the ages of 3 and 472 days. A record of the ulna is shown in figure 5. Note that all growth in all bones has occurred at the ends. The shots have remained the same distance apart.

In five bones the shots did not maintain fixed positions, as indicated by failure to remain the same distance apart throughout the growth. Apparently in each instance the shot at one end had been placed too centrally and had migrated within the medullary canal.

Of the remaining specimens, measurements were made of the humerus in four goats, of the radius in three, of the ulna in four, of the femur in three and of the tibia in three. The goat has no fibula. The measurements were converted into percentages, and the percentages were averaged. In no instance did the proportions of growth for the same bone in three or more animals vary more than 4 per cent.

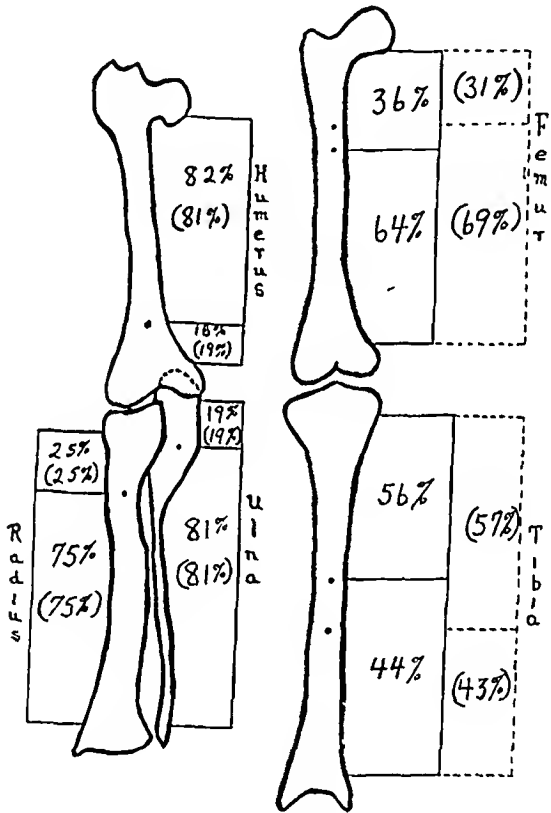


Fig. 3.—The percentages of proportionate longitudinal growth from each end of each principal long bone of a goat are charted as measured from experiments illustrated in figure 2. For comparison, the percentages for total growth for the same bones in man, as recorded by Digby, are included in parenthesis.

The average percentages for each bone are illustrated in figure 3 and the average actual measurements and percentages were as follows:

Bone	Number of Animals Used in Each Experiment	Average Growth, Mm.		Average Proportion of Growth, per Cent	
		Proximal End	Distal End	Proximal End	Distal End
Humerus.....	4	51	11	82.0	18.0
Radius.....	3	11	32	25.5	74.5
Ulna.....	4	20	72	18.8	81.2
Femur.....	3	29	52	35.8	64.2
Tibia.....	3	64	33	54.8	45.2

The accuracy of these measurements was affirmed by two control factors: 1. The shots remained the same distance apart throughout growth. 2. The total length of each bone was compared with the total length of its intact fellow on the opposite side. In no instance did these measurements vary more than 5 mm.; in four they were the same, and in thirteen there was a slight overgrowth of the bone subjected to operation. Obviously, neither the operation nor the presence of the shots near the epiphyseal lines had an appreciable influence on growth (fig. 2 A).

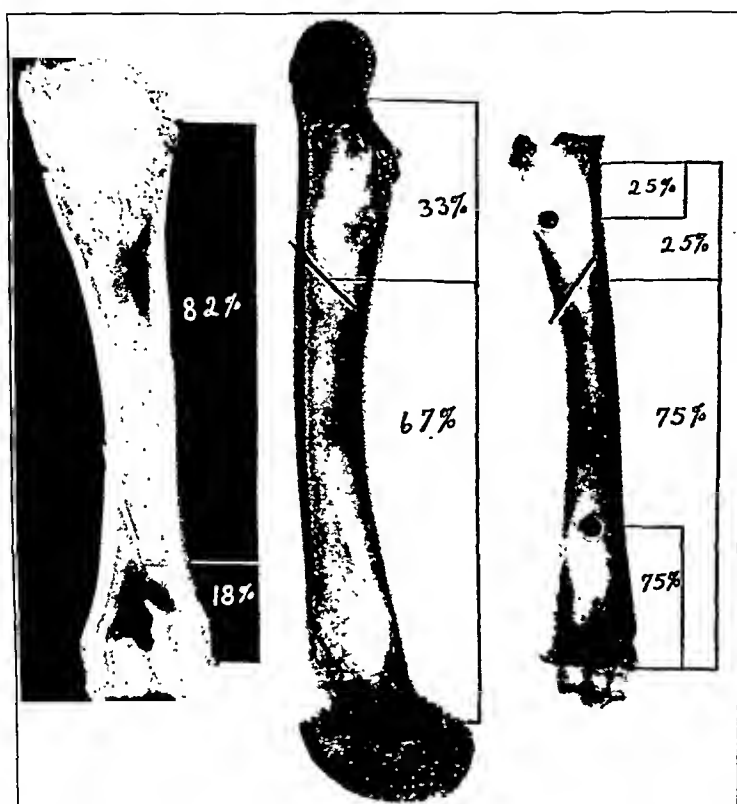


Fig. 4.—From left to right are the humerus, femur and radius of a goat 16 months old, illustrating the method used by Digby for determining percentages of growth. If one assumes that growth began at the point where the nutrient canal intersects the center of the medullary canal, the distance from this point to each end of the diaphysis represents the proportion of growth which has taken place at each end. For purposes of illustration pins have been inserted into the nutrient canals. As illustrated in the radius, the proportions of total growth determined by this method are the same as those of postnatal growth measured from the shots (table 1).

#### EXPERIMENT 3.—*Evaluation of Method of Digby.*

With accurate percentages of proportionate postnatal growth by controlled actual measurements, an evaluation of the method used by Digby to measure growth becomes a simple procedure.



Both the bones operated on and those used as controls (not operated on) were split longitudinally through the nutrient foramen. Each foramen was projected to a point where it intersected the center of the medullary canal. Measurements from this point to the end of each diaphysis were made. These measurements were converted into percentages, and the percentages were averaged. The principle involved in the method is illustrated in figure 4.

TABLE 1.—*Proportions of Growth in Percentage*

Period of Growth	Epiphyseal Lines to	Femur		Tibia		Humerus		Radius		Ulna	
		Proxi- mal	Dis- tal	Proxi- mal	Dis- tal	Proxi- mal	Dis- tal	Proxi- mal	Dis- tal	Proxi- mal	Dis- tal
I											
Prenatal	Phosphorus lines	38	62	49	51	83	17	24	76		
(New-born goats)	Nutrient canal (Digby)	42.7	57.3	42	58	60	40	20.4	69.6	33.3	66.6
II											
Postnatal (goats)	Shots	35.8	64.2	54.8	45.2	82	18	25.5	74.5	18.8	81.2
III											
Total Goat	Nutrient canal (Digby)	32.7	67.3	56	44	81.7	18.3	25.5	74.5	19.6	80.4
Human*		31.2	68.8	57.1	42.9	80.8	19.2	25	75	18.6	81.4

\* These figures are quoted from Digby.

TABLE 2.—*Growth of the Ulna of Goat 18 Over a Period of Sixteen Months\**

Age of Goat	Quantity of Growth					
	Proximal End			Distal End		
	Distance from Shots to Epiphyseal Line, Mm.	Net Growth		Distance from Shots to Epiphyseal Line, Mm.	Net Growth	
		Increase in Mm.	Proportion in per Cent		Increase in Mm.	Proportion in per Cent
4 days.....	3	..	..	7	..	..
32 days.....	6	3	23	17	10	77
60 days.....	8	2	23	24	7	77
90 days.....	10	2	23	31	7	77
118 days.....	12	2	25	37	6	75
148 days.....	13	1	25	40	3	75
180 days.....	14	1	25	43	3	75
Total	—	—	—	—	—	—
First six months.....		11			36	
490 days.....	20	6	14	82	39	86

\* Shots were placed in the ends of the ulna when the goat was 4 days old, 3 mm. from the proximal and 7 mm. from the distal epiphyseal line.

By comparison these percentages are almost identical with those obtained by actual measurements in experiment 2. Philogenetically it is of interest that the proportions of growth from each end of each long bone of the goat differ but slightly from those obtained by Digby<sup>11</sup> for adult human bones. For comparison these percentages have been compiled in table 1 and in figure 3.

#### EXPERIMENT 4.—*Rate of Growth.*

Humphrey<sup>6</sup> in 1861 observed that the epiphyseal cartilage at the end of the bone from which lesser growth takes place ossifies and closes earlier than the cartilage which contributes major growth. The latter cartilage Payton<sup>7</sup> constantly

found to be thicker. These observations were confirmed in this investigation and are well illustrated in figures 2 *B* and *D* and in figure 5.

In a study of longitudinal growth in madder-fed pigs Payton<sup>7</sup> observed that the rate of growth diminishes (1) as the period of growth advances and (2) more rapidly at the end which has the lesser increment. Our investigation bears out the first contention but not the second. We demonstrated that the relative proportion of growth from the two ends of a bone remains constant until the epiphyseal line which gives lesser growth begins to close. The results are illustrated in figure 5 and in table 2.

In analyzing table 2, it is apparent that growth from both ends was most active during the first four months of life and progressed at almost the same rate during this period. Growth from the distal end then suddenly became retarded to half its previous rate and continued at the new rate until the experiment was terminated.

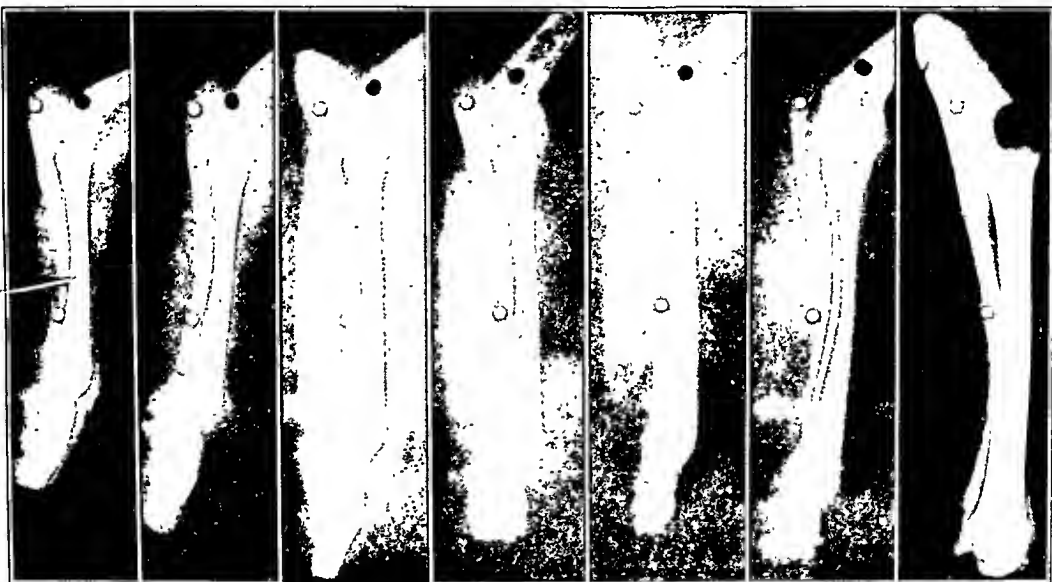


Fig. 5.—A series representing a progressive record of growth of the ulna of a goat, beginning with the third day after birth. The first five roentgenograms were taken at monthly intervals, the sixth at the seventh month, and the seventh at autopsy sixteen months after birth. Note that the rate of growth was rapid and constant for the first four months. It then slowed progressively with advancing age. The ratio between the two ends remained constant for six months.

Growth from the proximal end, however, showed a retardation as the cartilage began to ossify. The ratio of growth from the two ends for the first six months was constantly 3:1 (distal end, 75 per cent; proximal end, 25 per cent) and by the end of the subsequent ten months, 5:1. It will be noted also that the total growth from the two ends during the first six months was greater than that occurring during the subsequent ten months.

In general, the foregoing findings are applicable to all bones studied. The ulna, and the ulna in this particular goat (goat 18), was selected for illustration only because the series of roentgenographic records of it was technically superior for this purpose.

EXPERIMENT 5.—*Prenatal Growth.*

The investigation thus far has been concerned only with the longitudinal growth which occurs after birth. In order to make similar studies of prenatal growth it was necessary to find a method for marking the embryonic bones as soon after the beginning of ossification as possible. This was accomplished by producing phosphorus growth arrest lines.

Harris<sup>12</sup> has shown that starvation, severe and debilitating diseases, rickets and other nutritional and metabolic disturbances and chemical poisons frequently cause a temporary arrest of growth of bone. During this period the newly formed bone at each end and the adjacent cartilage become densely ossified, and when normal growth is resumed this layer of compact bone persists and casts in the roentgenogram a transverse line marking the site where growth had been temporarily arrested.

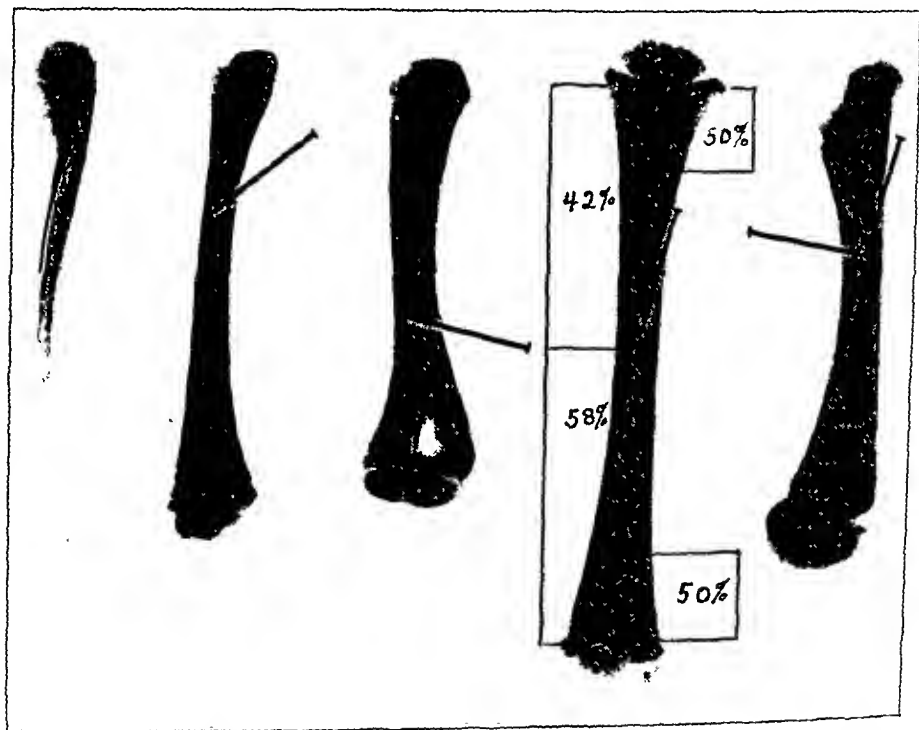


Fig. 6.—Principal long bones of a new-born goat, showing growth arrest lines produced by the feeding of phosphorus to the mother at the onset of pregnancy. The nutrient canals have been outlined with pins. The bones from left to right are: ulna, radius, humerus, tibia and femur. As illustrated in the tibia, prenatal growth measured both directly from the growth arrest lines and from the center of ossification shows that growth progresses more nearly equally from the two ends before than after birth.

As has been frequently noted following the original observation of Wegner,<sup>5</sup> feeding of phosphorus provides one of the most effective means of producing growth arrest lines. This suggested the plan of feeding phosphorus to pregnant animals in the hope that it would traverse the placenta and mark the bones of the fetus.

12. Harris, H. A.: Lines of Arrested Growth in the Long Bones in Childhood, *Brit. J. Radiol.* 4:561, 1931.

Three ewes were fed 1/25 grain of phosphorus (0.0026 Gm.) daily for six weeks beginning with the onset of pregnancy. One miscarried early, and each of the others delivered twins at term. Roentgenograms taken on the day following birth demonstrated two or more growth arrest lines at each end of each long bone in all four animals. Unfortunately, a line was not laid down early enough to mark the beginning of ossification. Considerable growth had taken place before the first one appeared. In order to obtain accurate measurements and to correlate these with measurements determined by the method of Digby, two were killed, and roentgenograms were made with nutrient canals outlined with pins (fig. 6). The measurements were converted into percentages, and the percentages were averaged. These are recorded in table 1.

The other two animals were reexamined a month after birth, and no vestige of the growth arrest lines remained. These lines, as pointed out by Harris,<sup>12</sup> may disappear promptly in very young, actively growing bone.

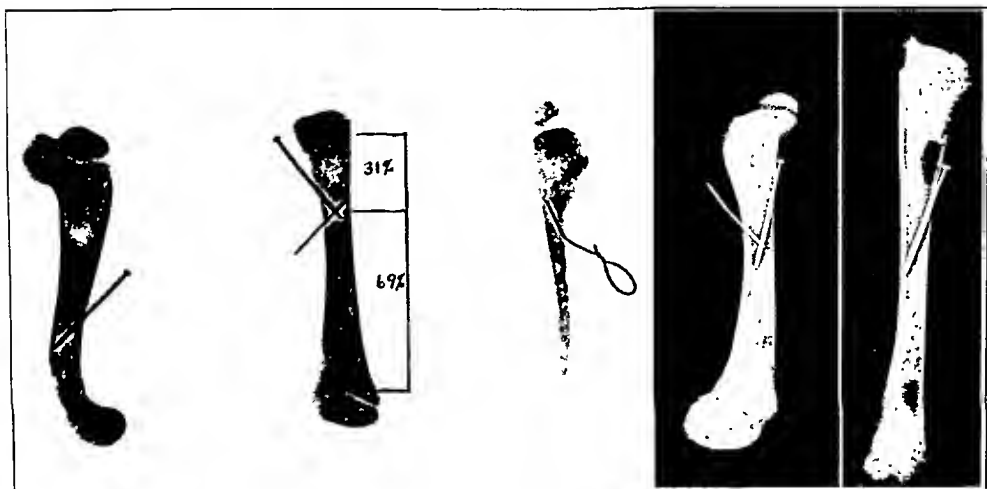


Fig. 7.—Principal long bones of a normal new-born goat. From left to right the bones are humerus, radius, ulna, femur and tibia. Note that prenatal growth is more equally proportioned between the two ends and also that the radius and femur each have two nutrient canals and that these intersect each other and the center of the medullary canal at the same point.

The results of this experiment showed that prenatal as well as postnatal longitudinal growth takes place at the two ends and that growth from the two ends is proportionately more nearly equal before than after birth and more nearly equal during the first portion of prenatal life. Except in the tibia, the distances from the center of primary ossification (determined by the method of Digby) to the first growth arrest lines were more equal than the distances from these lines to the epiphyseal lines. Thus, the ratios from the two ends for growth occurring after the appearance of the first lines more nearly equaled those of postnatal growth. It should be noted also that in bones provided with two nutrient canals these canals meet each other at a common point of intersection at the center of the medullary canal. This Digby interpreted as further evidence that ossification starts at the point where the nutrient canal intersects the center of the medullary canal.

In figure 7 are shown the bones of a normal new-born goat. A comparison of the measurements with those of the marked bones shows that the temporary arrest of growth produced by feeding of phosphorus to the mother did not alter the normal ratio of growth from the ends of the bones.

#### CONCLUSIONS

From the experimental evidence presented it is concluded that in goats:

1. All longitudinal growth of long bones, both prenatal and post-natal, takes place at the ends. Length is gained from the deposition of layers of new bone between the end of the diaphysis and the epiphyseal cartilage and between the articular cartilage and the epiphysis.

2. The proportion of longitudinal growth from the two ends of a long bone is unequal. The disproportion is greater for growth occurring after birth.

3. The rate of growth remains constant during the first four months, and then progresses at half its former rate. The epiphyseal cartilage, giving lesser increment, is the first to ossify and close.

4. The proportion of growth from each end of each long bone, as determined by actual measurements, is recorded. When converted into percentages these proportions are almost identical to those obtained by the method of Digby. We deduce, therefore, that the measurements of proportionate growth for human long bones as determined by Digby are accurate.

5. Growth arrest lines can be produced in the bones of a fetus by feeding phosphorus to the mother.

# A CLEAN INTESTINAL ANASTOMOSIS

## II. AN EXPERIMENTAL STUDY

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The great variety of technics that have been described and used for anastomosing bowel may seem to exclude the possibility of adding any further suggestions of merit. The very fact, however, that widely different methods can exist and have firm and prominent adherents implies that either there can be no superior procedure or it has not yet been presented. Eninent surgeons do not even agree as to whether the open or the closed form of operation should be adopted in performing entero-enterostomy in the large bowel. There seems to be a sort of fetishism among the more recently trained men requiring the use of the clean or closed method, while many of the best surgeons of the older school insist that better results follow the use of an open technic which permits accurate approximation of tissues without an undue "turn-in" forming a bulky cuff.

An analysis of these two basic methods reveals individual characteristics and fundamental differences. The closed technic tends to minimize soiling and infection but either fails to give good approximation or produces a considerable amount of traumatized tissue as a cuff, which subsequently becomes edematous and causes a temporary postoperative obstruction. This distention of swollen, friable bowel results in an uncontrollable amount of tension on the suture line which may prove disastrous. Frequently hemostasis is questionable. The open method affords the most accurate approximation of tissues with a minimum amount of inversion and cuff. No traumatized tissue need be inverted, and thus postoperative edema, distention, undue tension on sutures and obstruction are minimal. Varying amounts of soiling occur, and when segments of large bowel are sutured this may be considerable. Most patients are able to overcome a considerable amount of infection, but practically all patients with a temporary obstruction have stormy postoperative courses, and leaky suture lines result in abscesses, fistulas, or

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peritonitis and death. Were it possible to combine the good and eliminate the bad features of each method, a more acceptable procedure would present itself.

A closed technic which minimizes soiling, eliminates the inversion of traumatized tissue, allows accurate approximation, insures good hemostasis, permits the use of either silk or catgut for continuous or for interrupted sutures and is rapidly executed without demanding unusual dexterity will be outlined.

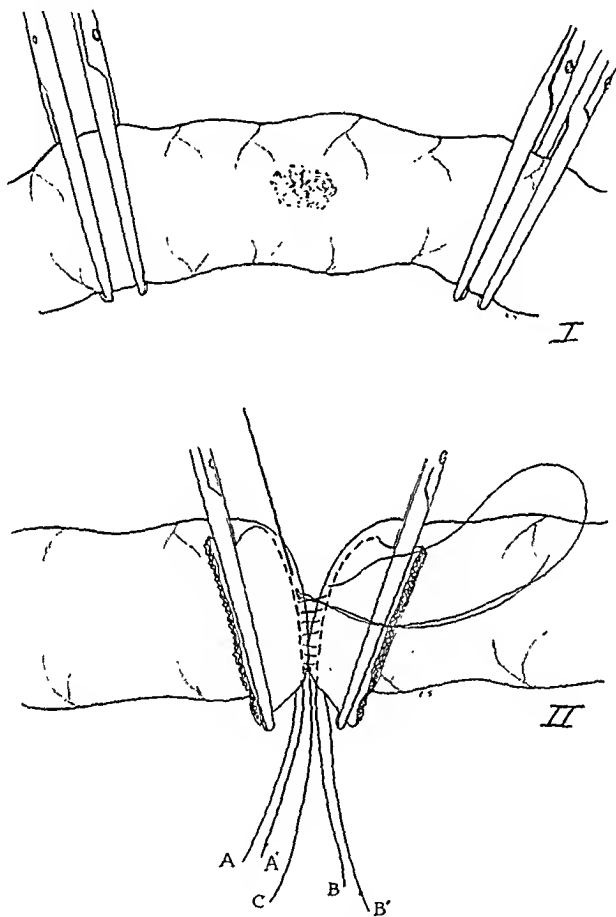


Fig. 1.—Antimesenteric views. *I* shows the clamps placed transversely across the bowel and perpendicularly to the mesenteric-antimesenteric diameter. *II* depicts the stage at which a segment of bowel has been removed, temporary purse-string sutures, *AA'* and *BB'*, are in place and a continuous posterior row is being laid down. Limbs *A'* and *B'* of the two purse-strings are marked with knots near their ends in order that they may be differentiated from *A* and *B* after the sutures are drawn up.

#### TECHNICAL PROCEDURE

The procedure is readily seen from the successive diagrams when supplemented by a few details. After the segment to be resected has been freed, crushing clamps are applied transversely, at right angles to the mesenteric-antimesenteric diameter, about 1.5 cm. from the chosen line of section. To obviate soiling by

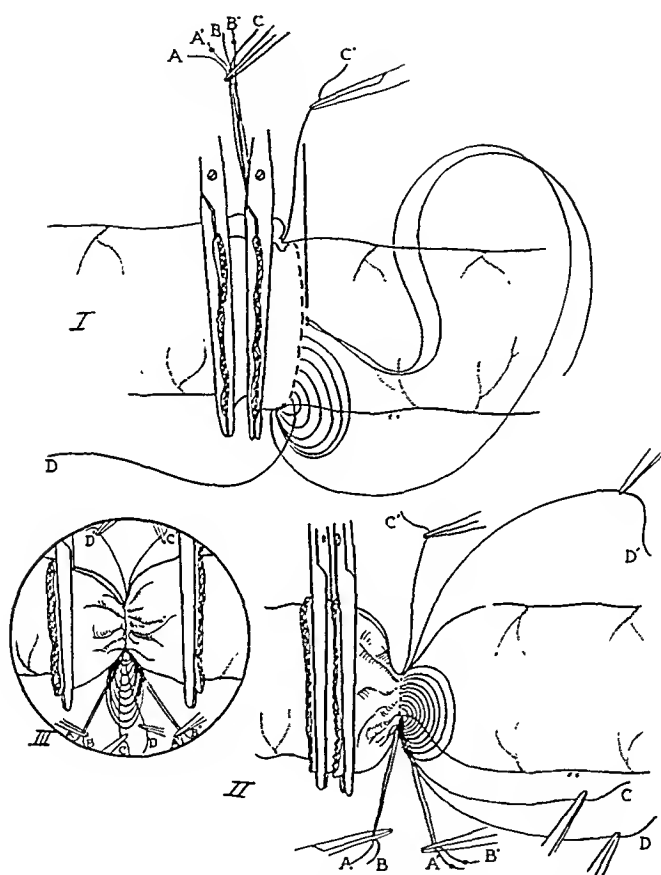


Fig. 2.—Antimesenteric views. *I* illustrates the situation after the posterior row has been pulled tight and both ends of the suture tied without constricting the lumen of the bowel, and a continuous anterior row of sutures is being placed. It is impossible to show the stitches in each segment of bowel. However, the row in the apposing segment is identical with the one shown in the figure. Sutures *A*, *A'*, *B*, *B'* and *C* have been laid across the bowel, on the posterior row of sutures, and between the two occluding clamps so as not to interfere with the placing of the anterior row. *II* shows the anterior suture, *DD'*, applied. While in actual practice the loops of the anterior suture are drawn snugly against the edges of the bowel, they are made long in the drawings to insure clear illustration. Neither end of this suture is tied. The purse-strings, *A-A'* and *B-B'*, are pulled up so as to close the bowel. Only one knot has been placed in each of the purse-strings so that they will pull up smoothly. They are not tied. *III* illustrates the appearance after the two occluding clamps have been separated to reveal the region of the inner posterior suture after the purse-strings have been drawn up.



forcing organisms through the wall of the crushed bowel, the serrated jaws of the clamps are treated with liquid phenol. This treatment is permissible since the tissues involved will be removed subsequently. The viscus is divided between the clamps, and the cut ends are cauterized with heat or phenol. Two purse-strings, ( $AA'$  and  $BB'$ , fig. 1) are placed at the levels selected for anastomosis, which should be about 1.5 cm. from the occluding clamps. This makes it possible to close the ends of the bowel later by drawing up these sutures before removing the clamps. However if it is inconvenient to sacrifice this additional length of bowel the purses-strings may be placed as near the clamps as desired. Deknatel surgical silk<sup>1</sup> no. 2 is the best material for these temporary sutures.

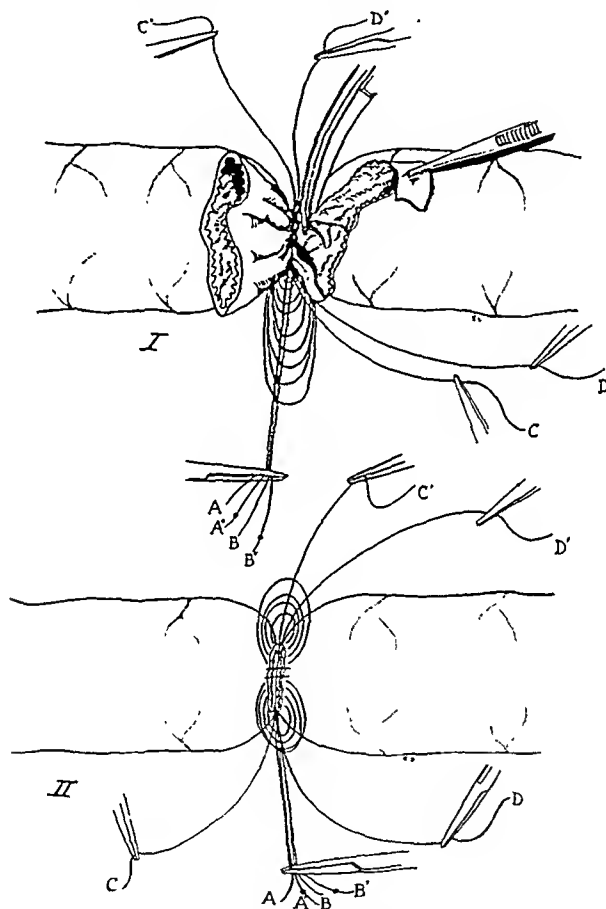


Fig. 3.—Antimesenteric views. *I* shows the stage at which the clamps have been removed successively, the mucous surfaces have been treated with liquid phenol, and the excess cuff is being trimmed off with scissors to about 2 mm. beyond the temporary purse-strings. Bleeding vessels are clamped and tied as they are encountered. *II* illustrates the stage at which the ends of the sutures  $A, A', B, B'$  and  $C$  are carried underneath the loops of the anterior row and the anterior suture,  $DD'$ , is pulled up beginning at its middle.

The inner posterior row of sutures ( $C$  in fig. 1, *II*) are placed close against the purse-strings. These sutures may be continuous or interrupted, and either silk

1. This silk may be obtained from J. A. Deknatel and Sons, Inc., Queens Village, L. I., N. Y.

or catgut may be used. The sutures are tied at once since the bowel is not constricted and the proper amount of tension can be applied. After the sutures ( $AA'$ ,  $BB'$  and  $C$ , fig. 2) are laid across the bowel on the posterior row and between the two occluding intestinal clamps the inner anterior line of sutures is placed. Either silk or catgut may be used, but whatever material is selected is best employed as a continuous suture. The loops of the suture between the successive stitches, which are taken so as to include a few fibers of submucosa, are carried around the edge of the bowel and under the ends of the clamps. If silk is used it is imperative that Deknatel surgical silk no. 1 or no. 2 be employed, because that silk is a hard, strong braided thread which slips through tissues

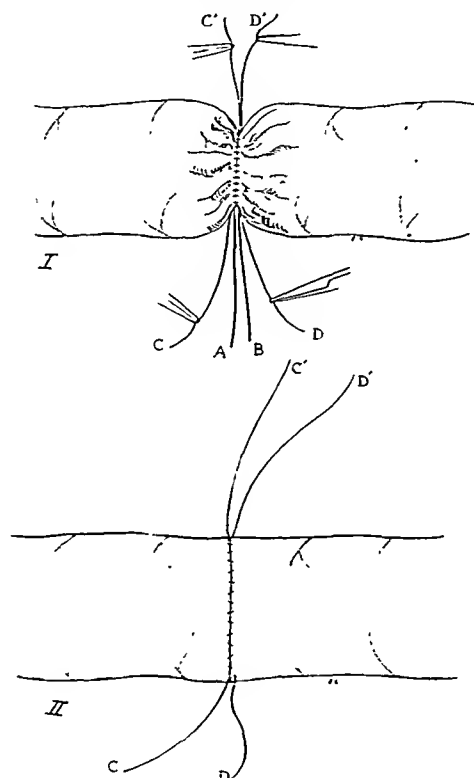


Fig. 4.—Antimesenteric views. *I* shows the stage at which the suture,  $DD'$ , of the anterior run has been pulled up, and one limb,  $A'$  and  $B'$ , of each purse-string has been cut short; *II*, the stage at which the temporary purse-strings have been withdrawn and the bowel has been opened out to its full diameter.

readily and does not fray. Since the diameter of the bowel is not constricted, it is possible to place all the sutures accurately even though the segments to be joined have different cross-sections.

After a single knot has been tied in each purse-string, the purse-strings are drawn up simultaneously to occlude the lumen of the viscus but not sufficiently tightly to interfere with free bleeding from the cut ends. The purse-strings must be pulled up simultaneously so as not to damage the posterior row of sutures. The intestinal clamps are removed successively, and the mucosal surface of each

cuff is treated thoroughly with liquid phenol. The cuff is trimmed to within approximately 2 mm. of the tightened purse-strings. This is easily accomplished, and care must be taken not to trim the edges too closely. Bleeding vessels are clamped and tied as they are encountered (fig. 3 I). When it proves necessary to place the purse-strings close to the clamps the contents of the bowel are milked back and restrained with digital pressure or rubber-shod intestinal clamps while the crushing clamps are removed and the purse-string sutures are pulled up. The purse-strings are not tied, except with a single knot, but this need cause no anxiety, as they show no tendency to loosen. The ends of the sutures *A, A', B, B'*

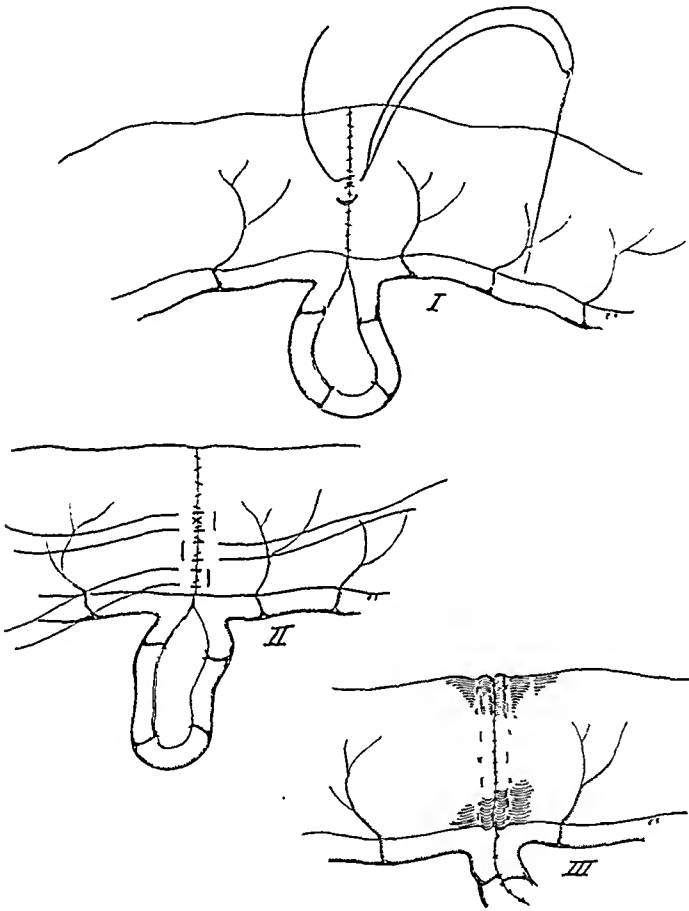


Fig. 5.—Side views. *I* shows the stage at which the anterior row is being tied so as to cover the knot of the posterior suture. Each end of the anterior row is secured in this manner. *II* shows the stage at which a second row of sutures is being placed, and *III*, the completed operation.

and *C*, are passed underneath the loops of the anterior suture *DD'* and the anterior row is pulled up, beginning at the middle as indicated in figure 3 II. Then one limb of each purse-string is cut short and the balance of the purse-strings withdrawn. The bowel is opened out to its normal diameter by gentle traction on *CC'* and manipulation of the constricted tissue (fig. 4 I and fig. 4 II). After each end of the anterior suture has been rethreaded, a stitch is taken so as to tie this suture and cover the knots of the posterior row. This completes the inner row. Any type of suture can be selected as a second, reenforcing row (fig. 5).

COMMENT

Obviously this procedure is the logical conclusion to a technic previously suggested by me.<sup>2</sup> While most of the underlying principles are the same as in the previous procedure, a simplified and more readily executed method of operation is presented. No traumatized tissue is turned in to form a massive cuff, which would become edematous and result in a temporary obstruction, stormy postoperative course and protracted convalescence. The amount of tissue inverted is under the complete control of the operator, since not more than 2 mm. of bowel need to extend beyond the inner row. Accurate approximation of corresponding portions of viscus is realized because all the anastomosing

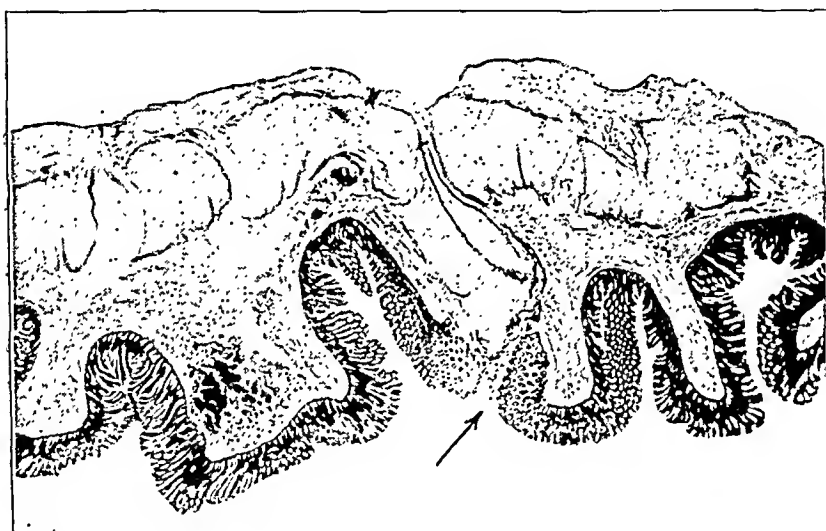


Fig. 6.—Photomicrograph ( $\times 10$ ) of a segment of the large bowel showing the relationship and accurate approximation of tissues immediately after the first row of sutures has been placed.

sutures are placed in nonconstricted sections of bowel. After the inner row of sutures is in place and the purse-strings are withdrawn the submucosa at the cut edge tends to retract and bring the opposing mucosal edges into close approximation. This completely covers the line of anastomosis on the side of the lumen with mucosa. The mucosal flaps form a perfect check valve against leakage into the peritoneal cavity and at the same time establish free drainage of the inner line of sutures into the lumen of the bowel (fig. 6). Bleeding is controlled by direct ligation of the vessels when the excess of cuff is cut away.

2. Poth, Edgar J.: A Clean Intestinal Anastomosis, *Arch. Surg.* **28**:1087 (June) 1934.

Since the lumen of the intestine is occluded by the purse-strings before the clamps are removed, soiling is reduced to a controllable minimum. Moreover, the purse-strings are simple devices which do not demand dextrous manipulations.

A large series of these operations have been performed on dogs in anastomosing segments of both large and small bowel; either silk or catgut or both have been used as continuous or as interrupted sutures, and end-to-end, side-to-side and end-to-side anastomoses have been established. All the animals have been followed closely over a period of months, and exploratory laparotomies have been performed from time to time. There have been no deaths due to peritonitis or obstruction. No stitch abscesses have occurred, and few adhesions have been found even in animals having three end-to-end sutures performed at the same sitting within a 5 inch (12.7 cm.) segment of the descending colon and sigmoid. Five months after operation no obvious or palpable thickening or constriction of the bowel has been found.

While almost any type of sutures desired may be employed, the following materials are preferable: (1) Deknatel surgical silk no. 2 for the purse-strings, (2) 00 chromic catgut on a swedged needle as a continuous suture for both the anterior and the posterior portion of the inner row and (3) fine black silk placed as a Halsted mattress stitch for a second row of anastomosing sutures.

# THE PENDULOUS HYPERTROPHIC BREAST

## COMPARATIVE VALUES OF PRESENT-DAY METHODS OF REPAIR AND THE PROCEDURE OF CHOICE

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The pendulous hypertrophic breast occurs far more often than is generally realized. It is frequent in young girls as well as in women who have borne children and may occasion great physical and mental distress. As a whole the medical profession has not taken cognizance of the prevalence or attendant discomforts of this condition, and many physicians are unaware that safe and successful methods of repair are available. It is my purpose briefly to classify and describe the etiology of the pendulous hypertrophic breast, to compare the principal surgical methods that are employed to correct this deformity and to present an operation in two stages that I consider the procedure of choice.

### CLASSIFICATION

It must be made clear at the outset that by the term hypertrophy is designated not only true hyperplasia of the mammary gland, which is rare, but various other forms of overdevelopment. In all there are four main types of hypertrophy of the breast: (*a*) true hypertrophy, which is rare; (*b*) fatty hypertrophy, the most common type; (*c*) hypertrophy as a result of mastitis (nodules and cystic fibroma), also a frequent variety, and (*d*) congenital relative hypertrophy, in which one breast is larger than the other.

It is extremely important to distinguish between the true hypertrophied breast and the ordinary oversized fatty breast, as the treatment and prognosis of the two conditions differ radically. True hypertrophy is characterized by a marked increase in the glandular structure and only a slight augmentation of fatty tissue. Most authors consider the true hypertrophied breast of puberty the characteristic type. The enlargement starts inconspicuously between the ages of 14 and 16 and then develops rapidly, reaching the climax within a few months. The breast attains enormous proportions, often extending below the umbilicus and to the pubis, and there are frequently concomitant disturbances in the general health.

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To this type may be added another form of true hypertrophy which occasionally appears during pregnancy. This variety is rarer than the true hypertrophy of puberty, but it has similar clinical manifestations. It differs from the first type chiefly in its time of onset and in the fact that it is likely to diminish spontaneously after childbirth.

Far more common than true hypertrophy is hypertrophy with fatty degeneration, which often has no relation to generalized adiposis. In this condition the breasts become enlarged at an early age and gradually increase, their augmented weight producing ptosis. Fatty tissue, which is present throughout the breast, predominates in the lower portion, especially in the external quadrant. Glandular tissue is scarce and is usually seen at the bottom of the ptosed breast sac (fig. 1).

Another type of hypertrophy of the breast which is often seen is that caused by mastitis. In these cases the breast is invaded by multiple nodules (cystic fibroma or fibro-adenoma), varying in size and number.

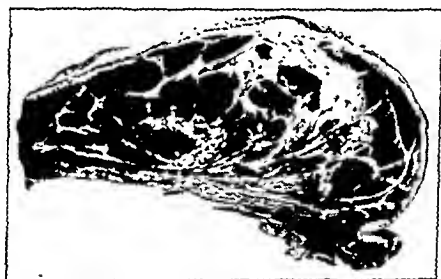


Fig. 1.—Section taken from a hypertrophic breast. The light parts represent glandular structures; the dark, fatty tissue (from Joseph).

Frequently in this form of hypertrophy the breasts are asymmetrical, owing to an unequal development of the mastitis. In one of my cases in which the condition was due to this cause, the left breast was about one-third larger than the right (fig. 7).

Among the congenital types of hypertrophy the only abnormality common enough to warrant comment is mammary asymmetry. Needless to say, I am not speaking of minor diversities in size which are present in the breasts of virtually every woman. I am concerned here only with the cases of marked asymmetry, in which one breast is conspicuously enlarged. Usually these malformations are associated with other anatomic abnormalities of the thoracic wall or of the extremities. Two of my patients showed definite thoracic maldevelopment on the side of the larger breast.<sup>1</sup>

1. Maliniak, J. W.: Asymmetrical Breast Deformities, *Ann. Surg.* 99:743 (May) 1934.

## ETIOLOGY

True hypertrophy of the breast is a pathologic manifestation the cause of which is not yet known.

In fatty hypertrophy there is undoubtedly a strong hereditary factor. Enlarged, pendulous breasts are frequently observed in several successive generations.

That there is an endocrine contribution also seems likely. The relationship between the mammary glands and the ovaries is indisputable; the physiologic and anatomic changes occurring in the breast at puberty are strongly influenced by hormones of internal secretion. It seems highly probable that an excess of these hormones accelerates the development of the breast.

Hypertrophy which is the result of mastitis is, of course, due to the factors responsible for the mastitis. The underlying cause is often trauma of some kind, such as repeated lactation or pressure from tight brassières.

There is considerable evidence in support of the theory that prenatal maldevelopment is an important etiologic factor in the production of asymmetry of the breast. While associated malformations are not, as a rule, present in cases of the common varieties, extreme types usually present accompanying abnormalities.<sup>1</sup>

The mechanism of ptosis is easily understood. Mammary prolapse is a natural phenomenon in woman, occurring as the weight of the breast increases and its supporting structures become distended. A rapid increase in the volume and weight of the breast hastens the natural tendency to prolapse; the base of the breast is shifted downward, and the skin and suspensory ligaments are stretched. Pregnancy and lactation accentuate these factors.

Lack of proper support is another important element. False modesty often constrains girls at puberty to suppress their normally developing breasts by tight brassières, or, as in the postwar period, fashion may decree a boyishly flat chest, the semblance of which can be achieved only by a compressive bandeau. At the same time that the bandeau flattens the breasts it pulls them downward, stretching the skin and suspensory ligaments. It is natural that girls should seek to conceal abnormally large breasts, but the tight brassières which they use to achieve this purpose merely increase the ptosis. A proper support raises the breasts to their normal position but of course displays their proportions. In almost all my cases there was a history of early sensitiveness and the use of restrictive brassières to conceal the overdeveloped breasts.

## CONSIDERATIONS OF SURGICAL TREATMENT

*Indications for Surgical Intervention.*—Naturally not all large breasts should be submitted indiscriminately to surgical treatment, and the oper-



ative indications should be carefully considered in each case. The following factors are of prime importance in reaching a decision: the degree of deformity; the age of the patient and her attitude toward the malformation; the influence of the abnormality on systemic health, and the extent to which it interferes with normal social and economic life.

Although fatty hypertrophy cannot be considered a pathologic manifestation, it may indirectly exercise an adverse effect on the general health. Traction on the muscles and skin of the shoulders and thoracic region causes pain and produces faulty posture. The heavy breasts make activity difficult; the women become sedentary in their habits, and adiposity and general sluggishness result. Because of excessive perspiration and disturbed circulation, dermatitis develops in the submammary region. This condition demands continual care, particularly in warm weather. The presence of these distressing conditions is a warrant for surgical treatment.

*Alleged Contraindications.*—For some reason the question of plastic repair of the breast is rarely discussed in medical literature, and when it is considered the result is more likely to be confusion than clarification. As a consequence, hypertrophy of the breast often appears to be misunderstood, and fallacious arguments are advanced against surgical procedure for relief of the condition, which do not stand the test of searching analysis.

The first charge that is brought against operative reconstruction of the breasts is disturbance of mammary function. It is true that most breasts do not lactate after plastic repair, but, on the other hand, the pendulous hypertrophic mamma per se is rarely capable of lactation. Surgical treatment, therefore, cannot be held responsible for the absence of function in this kind of breast.

The question of conspicuous scarring has also been raised, but this too has no validity as a deterrent to surgical treatment. In the procedure of choice, which will be described later in this paper, the principal scar is placed in the submammary fold.

These considerations do not, of course, enter into the surgical treatment of true hypertrophy. In this condition amputation affords the only hope of relief. An attempt to simulate the normal appearance of the chest can be made in these cases by a free graft of the nipple and areola from the amputated breast.<sup>2</sup> The surgical principle is less drastic and more hopeful in the correction of other types of hypertrophy.

2. Dartigues, L.: De la greffe autoplastique libre aréolo-mamelonnaire, combinée à la mammectomie bilatérale totale: Les raisons de sa prise, *Paris chir* 2:11 (Jan.) 1929.

*Requirements for Successful Repair.*—To constitute an acceptable method of repair, the procedure for the correction of a pendulous hypertrophic breast should embrace the following concepts:

1. The blood supply of the breast must be preserved in order to prevent partial necrosis.
2. Extensive injury to the galactophorous ducts should be avoided in order to preserve partial mammary function when possible.
3. The gland must be firmly affixed in its new location to prevent recurrence.
4. There should be no conspicuous scarring.
5. All the diameters of the breast must be reduced proportionately to insure an esthetic end-result.

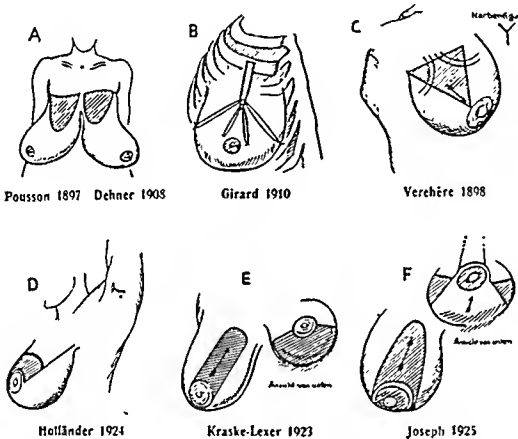


Fig. 2.—Diagrams showing procedures for the plastic repair of the hypertrophic breast now rarely used. Diagrams *A*, *C* and *D* show the enlarged breast raised, following excision of the skin by various procedures; *B* shows the disk-shaped excision of glandular tissue through the submammary fold and the affixation of the gland to the rib and fascia, and *E* and *F* illustrate the open transposition of the areola to a higher location with and without a pedicle. These procedures, originated by Lexer and Kraske and by Joseph, are still in use with some modifications.

These criteria must be borne in mind in the evaluation of the various surgical procedures which I am about to describe.

#### COMPARISON OF SURGICAL METHODS

Without regard to the numerous modifications that have been made, there are two main procedures for the correction of the pendulous hypertrophic breast: the method of transposing the nipple through a buttonhole incision and the method of open transposition. Proper evaluation of these procedures necessitates the consideration of the evolution of each of these methods (fig. 2).

In 1909 Morestin described before the French Academy of Medicine the plastic repair of hypertrophic breasts by the removal, through an incision made in the submammary fold, of a disk-shaped segment from the posterior aspect of the gland.<sup>3</sup> This procedure was apparently applied to overdeveloped, protruding breasts which had to be flattened. He made no mention in this communication of the use of a buttonhole incision for transposition of the nipple; but Villandre,<sup>4</sup> referring in 1925 to a patient on whom he had operated in 1911, gave Morestin credit for the procedure.

In 1910 Girard,<sup>5</sup> in a communication before the International Congress of Surgery in Berlin, presented a method of plastic repair similar to that of Morestin and of Dehner;<sup>6</sup> he removed excessive fat and glandular tissue through an incision in the submammary fold and affixed the upper pole of the gland to the rib. Lotsch<sup>7</sup> in 1923 published a procedure similar to that attributed to Morestin; he transposed the nipple to a higher position but made an additional vertical incision in the midline. This modification had the disadvantage of leaving a conspicuous scar on the lower pole of the breast, but it made possible a more accurate adjustment of the excessive skin.

In 1925 Passot<sup>8</sup> and Dufourmentel,<sup>9</sup> pupils of Morestin, published a procedure for the plastic repair of the breast by transposition of the nipple through a buttonhole incision. Reduction and transposition of the mamma were done in a single operation. Axhausen<sup>10</sup> reported a similar method in 1926.

The procedures described by Kraske<sup>11</sup> and by Joseph<sup>12</sup> in 1923 and 1925, respectively, were based on open transposition of the nipple to a higher location after excision of an oblong fragment of skin. Joseph left a cutaneous bridge attached to the areola to insure its blood supply. Lexer made a circular incision around the areola, transposing it upward.

3. Morestin: Hypertrophie mammaire unilatérale corrigée par la résection discoïde, *Bull. et mém. Soc. d. chirurgiens de Paris* **35**:996 (Oct. 20) 1909.

4. Villandre, cited by Dartigues, L.: *Arch. franco-belges de chir.* **28**:325, 1925.

5. Girard, C.: Mastoptose und Mastopexie, *Verhandl. d. deutsch. Gesellsch. f. Chir.* **39**:200, 1910.

6. Dehner: Mastopexie zur Beseitigung der Hängebrust, *München. med. Wchnschr.* **55**:1878, 1908.

7. Lotsch, Fritz: Ueber Hängebrustplastik, *Berl. Gesellsch. f. Chir.*, May 14, 1923; abstr., *Zentralbl. f. Chir.* **50**:1241, 1923.

8. Passot, R.: La correction esthétique du prolapsus mammaire par le procédé de la transposition du mamelon, *Presse méd.* **33**:317, 1925.

9. Dufourmentel, L.: *Bull. et mém. Soc. d. chirurgiens de Paris* **17**:219, 1925.

10. Axhausen, G.: Ueber Mammoplastik, *Med. Klin.* **22**:976, 1926.

11. Kraske, H.: Operation der atrophischen und hypertrophischen Hängebrust, *München. med. Wchnschr.* **70**:672, 1923.

12. Joseph, J.: Zur Operation der hypertrophischen Hängebrust, *Deutsche med. Wchnschr.* **51**:1103, 1925.

and removed the excessive fat and glandular tissue principally from the lower pole (fig. 2). Biesenberger<sup>13</sup> reduced the breast to one-half its original size by removing the external half of the gland and rotating upward the lower end of the inner half. It is unnecessary to mention other methods which have been suggested. The principal ones have already been outlined and furnish sufficient material for consideration before discussing the procedure of choice. The German methods may first be considered.

*Method of Joseph.*—To the least critical eye it is apparent that the method of Joseph is unnecessarily complicated and inflicts much needless scarring. By merely excising the skin above the nipple and

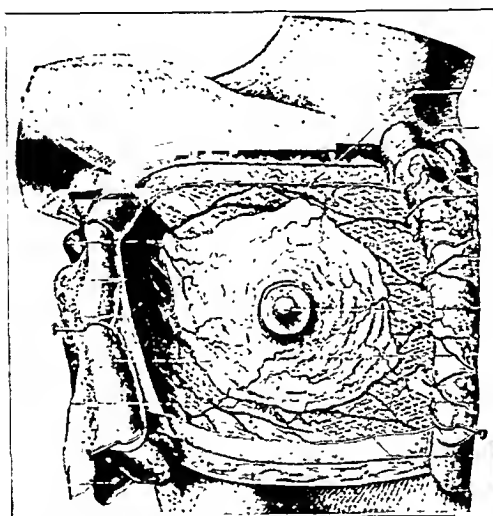


Fig. 3.—Drawing showing the main blood supply of the glands of the breast provided by the thoracic lateral and internal mammary arteries (from Testut). The blood supply must be preserved during transposition of the areola in the procedure of choice.

shifting the latter structure to a higher position, he obtained a purely cutaneous suspension of the central portion of the gland without affixation to the deeper structures. Ideal modeling of the breast in all diameters is impossible, and there is strong likelihood of recurrence of ptosis. Joseph's use of a cutaneous bridge proceeded from his belief that the circular incision around the areola interferes with the blood supply of the nipple and may cause necrosis. This, however, has not been the experience of the majority of surgeons using the circular incision, for the nipple derives its principal blood supply from the thoracic and the

13. Biesenberger, cited by Joseph.<sup>14</sup>

internal mammary artery, and no sloughing occurs if these channels are preserved (fig. 3).

Joseph later modified his method and adopted an operation in two stages.<sup>14</sup> In the first stage, instead of transposing the nipple openly, he transferred the areola subcutaneously on a pedicle into a resected window (fig. 4). The pedicle was detached from the transposed nipple in a second operation. Aside from the fact that this method invites infection by leaving skin in contact with a raw surface, it is an unnecessary precaution since the nipple derives its main blood supply not from the skin but from the interior blood vessels.

*Method of Lexer and Krasko* (fig. 2).—Since in this procedure the excess of fat and glandular tissue is removed by a vertical crescentic excision from the lower pole of the breast, extending from the nipple to the submammary fold, the closure of the resulting defect causes the breast to protrude conspicuously. The suspension of the gland is purely cutaneous, thus producing a predisposition to recurrence of the



Fig. 4.—In diagrams *A* and *B* is shown the modified procedure of Joseph in which the diminished areola is transposed on a pedicle in a buttonhole under a small cutaneous bridge (*a, b, c* and *d*). In *C*, after complete healing the lower half of the areola is shown detached from the pedicle and sutured to the upper border (*a-b* of *B*) of the cutaneous bridge. The hypertrophic parts of the breast are excised, and the lower border of the bridge (*c-d* of *B*) is sutured in the submammary fold.

ptosis. The end-result is further subject to criticism from the esthetic standpoint because of the impossibility of modeling the breast accurately in all diameters.

*Method of Biesenberger* (fig. 5).—The method of Biesenberger, which reduces the breast by the excision of its external half, ingenious as it is, appears to be attended by certain risks. Since suppression of an important part of the blood supply may produce necrosis, it seems somewhat risky to abolish the thoracic lateral artery and depend solely on the internal mammary artery for the vitality of the areola and the remaining tissue of the breast. In addition, to my mind,

14. Joseph, J.: *Nasenplastik und sonstige Gesichtplastik nebst Mammaplastik*, Leipzig, Curt Kabitzsch, 1930, vol. 3, p. 791.

torsion of the pedicle is an unwelcome possibility in the rotation of the lower pole of the inner half of the gland around the center. Apparently this procedure is safe in the hands of its author, but the potential danger of necrosis looms large in my mind.

*Procedure by a Buttonhole Incision.*—The procedure by buttonhole incision, originated by Morestin and Villandre and subsequently adopted with modifications by Dufourmentel,<sup>9</sup> Dartigues,<sup>15</sup> Passot<sup>8</sup> and myself,<sup>16</sup> is free from most of the objections that can be raised against other methods. A large flap is made on the anterior aspect of the breast, and all the skin is removed from the posterior surface, permitting reduction and modeling the breast in all diameters. The nipple and areola are inserted into a buttonhole incision in the anterior flap, and the gland, around which a circular incision has been made, is firmly affixed to the pectoral fascia, preventing recurrence of ptosis. Scarring is minimized by suturing the flap into the submammary fold (fig. 6). When this

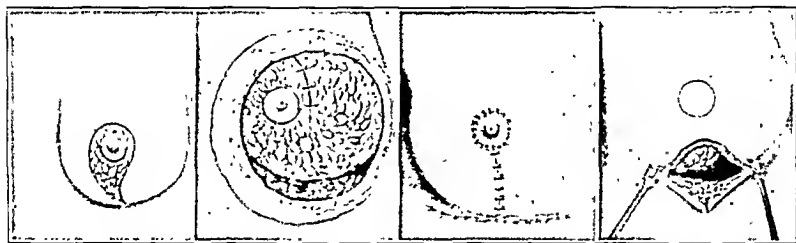


Fig. 5.—Drawing showing the steps in the procedure of Biesenberger in which the extreme half of the breast is excised and the lower pole of the remaining half is turned upward to produce a spherical shape. According to the author, the two breasts are reconstructed in one stage.

operation is performed in one stage, as it originally was done by the followers of Morestin, there is no doubt that the danger of necrosis is present. I myself had peripheral necrosis of the skin in several of my first patients, sometimes only along the line of suture but in one case over an extensive area below the nipple, between the buttonhole and the submammary fold, in which the blood supply is not of the best and the tension is greatest (fig. 6). Tension, it may be said, is one of the chief factors in this complication. In two cases in which the breasts were large and pendulous but without much fat, necrosis

15. Dartigues, L.: Traitement du prolapsus mammaire, Arch. franco-belges de chir. 28:313 (April) 1925.

16. Maliniak, J.: Pendulous Breast: Etiological Factors and Surgical Treatment, Comptes rendus de la Congrès de la Société française de chirurgie réparatrice, plastique et esthétique, Paris, Norbert Maloine, 1931.

of the nipple occurred on one side. This was due to the removal of much glandular tissue, especially in the external quadrant, necessitating ligation of some of the branches of the thoracic lateral artery.

Preservation of the blood supply is of the utmost importance in the prevention of necrosis, and discoloration of the nipple is a warning which should not be disregarded (fig. 3). In two of my patients the transposed nipple promptly became cyanotic, and normal color did not return even after prolonged application of heat, as often happens if the blood supply has been preserved. If discoloration is the product of tension, this should be immediately relieved.

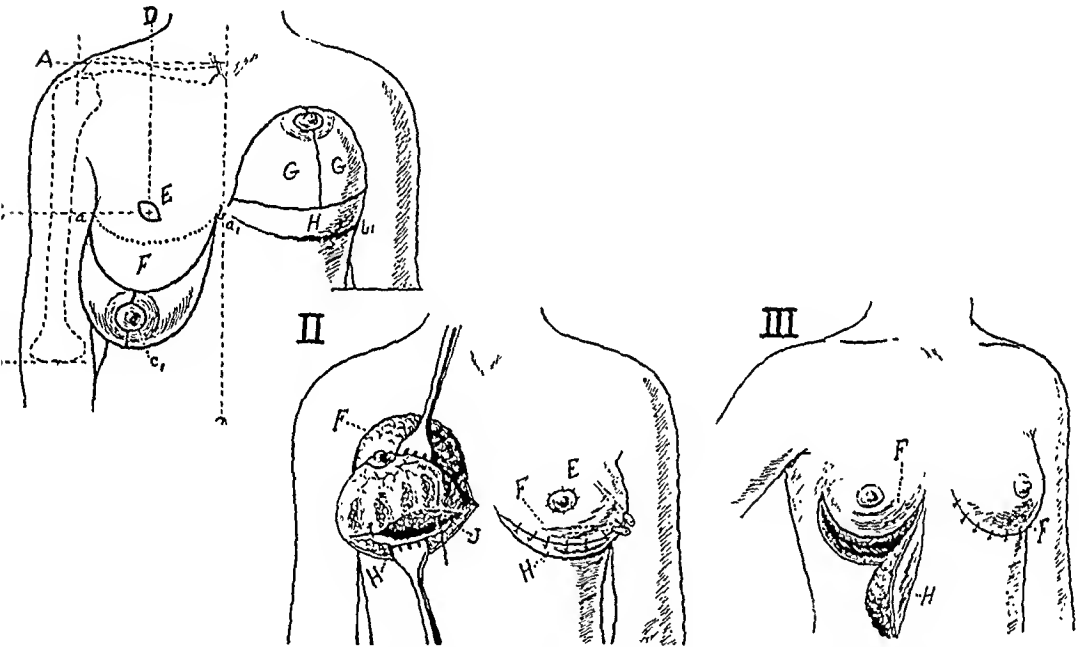


Fig. 6.—Diagrams illustrating the procedure of choice—the two stage method—for the repair of a hypertrophic breast. In diagram I horizontal lines are drawn (A) across the clavicle, (B) through the elbow joint and (C) half-way between A and B; a vertical line (D) is drawn through the middle point of the clavicle. Point E, the intersection of C and D, determines the new location of the nipple. F represents the anterior flap extending to the areola; G, the excessive skin around the areola; H, the flap of skin on the posterior aspect of the breast to be sutured to flap F, and a-b, the submammary fold. The flaps are outlined to bring about the covering of the reduced breast without tension. The areola is transposed and sutured into a buttonhole (E) made in the anterior flap (F). The incision on the posterior aspect of the breast is made above the submammary fold (a-b), outlining a flap (H) to be sutured to flap F. In diagram II are shown the closure of the defect in the right breast and the appearance of the left breast after transposition of the areola and suturing of the flaps of skin. In diagram III are shown the removal of excessive skin, fat and glandular tissue by a crescent-shaped excision along the submammary fold (right breast) and the final condition after closure of the defect (left breast).

If only the skin is necrosed, the damage is not as great as when necrosis of the nipple occurs. In the former contingency the defect is epidermized after sloughing has taken place, and the resultant scar can be easily eradicated. When the nipple sloughs, it cannot be replaced.

Torsion of the pedicle is another important cause of necrosis. It can be avoided by taking suitable precautions against rotating the pedicle as the nipple and gland are transposed.

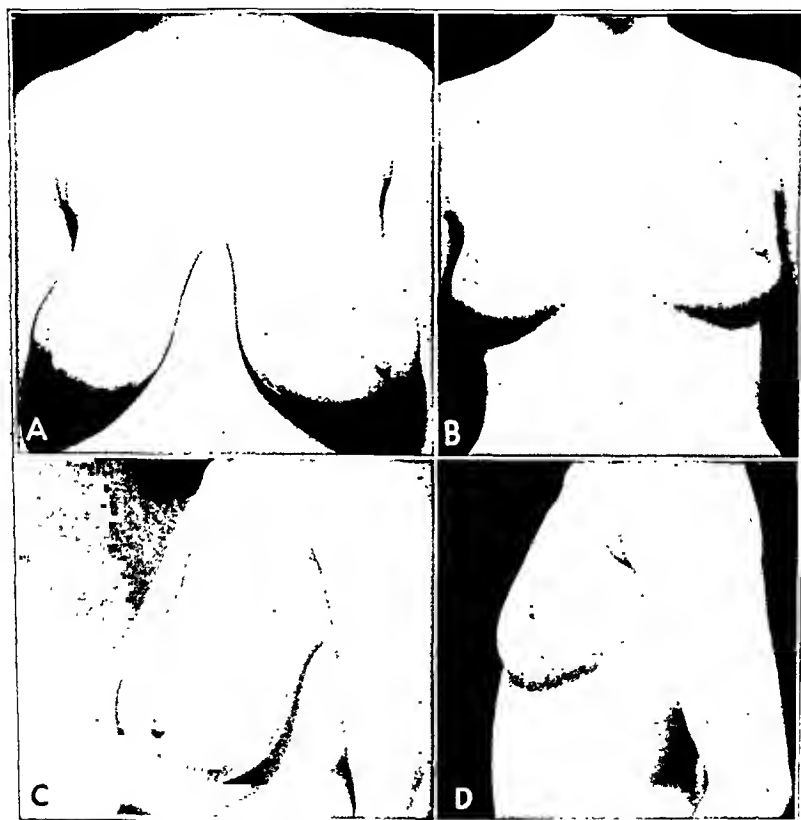


Fig. 7.—In *A* and *C* is shown hypertrophy of the breasts in a case of bilateral cystic mastitis occurring in a girl of 23. Both breasts were considerably oversized at the age of 16 and became particularly enlarged and painful at the age of 22. Unbearable physical discomfort rendered reconstruction urgent. In *B* and *D* is shown the appearance following plastic repair done in two stages.

*Method of Choice.*—The few early cases of necrosis which I have described prompted me to abandon the one stage procedure in favor of a method which would preserve the blood supply as completely as possible and avoid tension during transposition of the areola. The two stage operation which I am now using as the method of choice has



satisfactorily solved the problem for me. Since its adoption I have never had the slightest sign of necrosis of the skin or nipple in any of my cases.<sup>17</sup>

The first stage of the repair is limited to transposition of the partially diminished breast (fig. 6). A circular incision is made around the

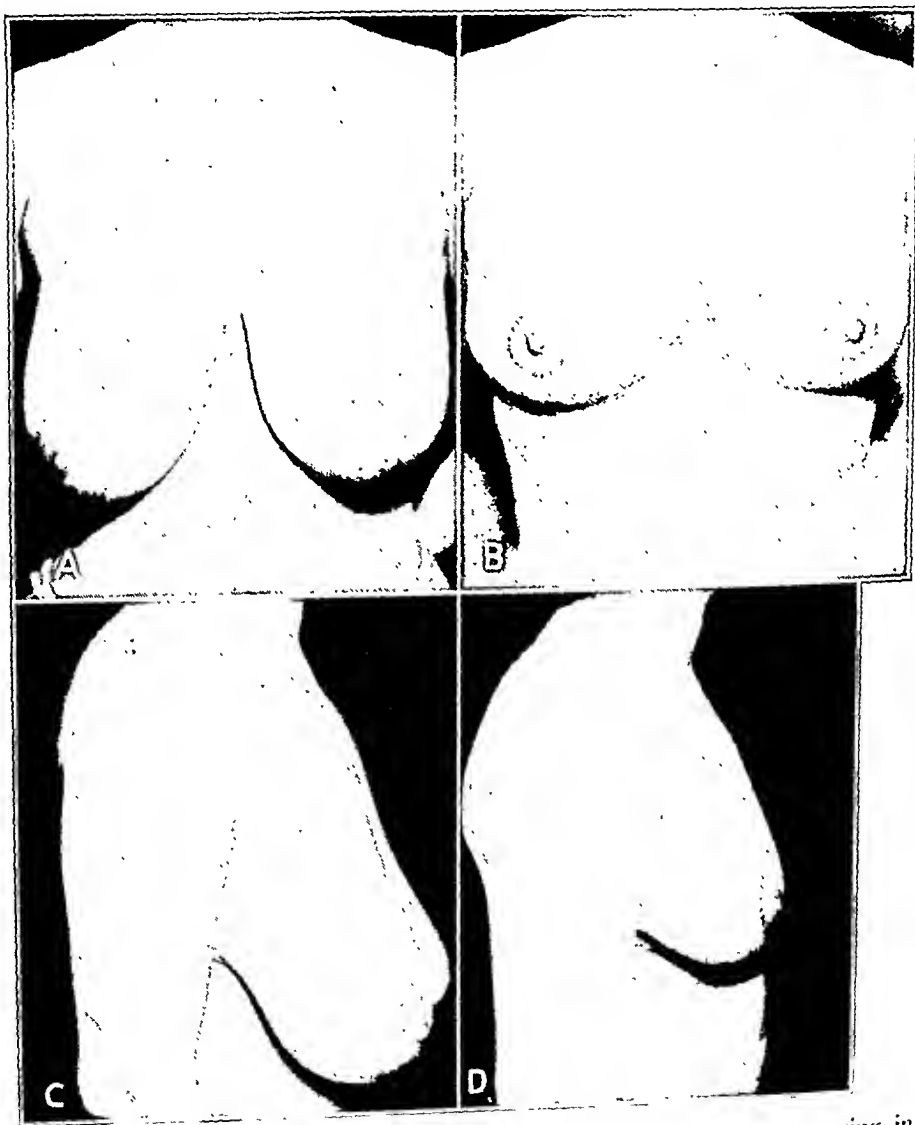


Fig. 8.—*A* and *C* show the hypertrophic and pendulous breasts occurring in a married woman of 28 which greatly interfered with her profession as pianist. Repair was done by the two stage procedure. In *B* and *D* is shown the final result a few weeks after the second stage of the operation.

areola, reducing it to the normal size. A concave incision on the anterior aspect of the breast reaches from one side of the submammary fold

17. Maliniak, J.: The Pendulous Hypertrophic Breast, *Am. J. Surg.*, to be published; footnote 1.

to the other. A flap is separated, extending as high as the second intercostal space, and a buttonhole incision is made into which the areola is sutured. In most cases the upper pole of the breast is affixed to the pectoral fascia before suturing of the areola. The skin is removed from the posterior surface of the breast to an extent determined in each case by the size of the transposed organ, the chief consideration being the avoidance of tension on the lines of suture. Hematoma is prevented by drainage of the undermined area through the external angle of the incision. There is no disturbance of the blood supply in the external quadrant. If reduction of the gland is performed at the first operation, it is limited to the lower pole. The branches of the internal mammary artery on the inner side of the breast are usually left undisturbed.

In thirty breasts corrected in this way, not once did cyanosis of the nipple or necrosis of the skin occur. The color of the nipple was gratifyingly reassuring immediately after transposition, in striking contrast to that in my experience with the one stage operation.

The second stage is carried out from four to six weeks later, when the nipple has completely "taken" in its new location. The excess skin, fat and glandular tissue are removed through a crescent-shaped excision in the submammary fold.

When correction is bilateral, this procedure does not lengthen the surgical period. In the one stage operation the correction is usually done separately on each breast, thus requiring two surgical periods for completion. If one performs the first stage of the operation on each breast at the same time, as I do, the repair on the two breasts is finished together, and the total time required for reconstruction is the same as with the one stage method (figs. 7 and 8).

#### SUMMARY AND CONCLUSIONS

1. The pendulous hypertrophic breast is more common than is generally believed, in young girls as well as in women, and occasions both mental and physical distress. There are four main types—true hypertrophy, fatty hypertrophy, hypertrophy resulting from mastitis and congenital asymmetry.

2. Among the etiologic factors are embryonic maldevelopment, heredity, endocrine disturbances, repeated pregnancies and periods of lactation and trauma.

3. The suppression of mammary function is not a contraindication for reconstruction, as normal function is rarely present in the pendulous hypertrophic breast.

4. The procedure of choice is a two stage method. The first stage consists of transposition of the partially reduced breast, with preservation of the blood supply and avoidance of tension. Excision of the remaining excessive skin, fat and glandular tissue is done in the second stage after the nipple has "taken."

5. The two stage procedure is a safe method for the correction of a common and distressing deformity. The danger of necrosis is entirely eliminated, and the end-result is assured. There is no conspicuous scarring, since the main scar is concealed in the submammary fold.

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## MULTIPLE MENINGIOMAS

REPORT OF A CASE IN WHICH THREE INTRACRANIAL MENINGIOMAS WERE REMOVED SUCCESSFULLY

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Meningioma, which constitutes from 10 to 15 per cent <sup>1</sup> of the tumors found within the cranial cavity, usually occurs singly, although the occurrence of multiple intracranial meningiomas is by no means unknown. Hosoi,<sup>2</sup> in 1930, reviewed the literature and reported twenty-two cases of multiple meningiomas, including one of his own (see table).

A case not included in Hosoi's list was reported by von Anfinow <sup>3</sup> in 1889. The patient, a man 36 years old, was found at necropsy to have four large and many small dural endotheliomas. There was no mention made of associated tumors of other types.

In 1932 Üprus <sup>4</sup> reported the finding of ten intracranial meningiomas in a patient who had suffered for fifteen years with headaches and vomiting. List,<sup>5</sup> in 1933, likewise found multiple meningiomas at necropsy in a woman, 53 years old, who had undergone exploratory operation for a cerebellar tumor. Von der Hütten <sup>6</sup> described the case of a woman, aged 30, who had complained for four months of increasing

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1. H. W. Cushing (Intracranial Tumors: Notes upon a Series of Two Thousand Verified Cases with Surgical-Mortality Percentages Pertaining Thereto. Springfield, Ill., Charles C. Thomas, Publisher, 1932) estimated that meningiomas constitute 13.4 per cent of the intracranial tumors. H. W. Cushing and Percival Bailey (Tumors Arising from the Blood Vessels of the Brain: Angiomatous Malformations and Hemangioblastomas, Springfield, Ill., Charles C. Thomas, Publisher, 1928) estimated an incidence of 12.22 per cent, and Craig, 14.9 per cent.

2. Hosoi, K.: Meningiomas with Special Reference to Multiple Intracranial Type, *Am. J. Path.* 6:245 (May) 1930.

3. von Anfinow, J.: Ein Fall multipler Geschwülste in der Schädelhöhle, *Neurol. Centralbl.* 8:585 (Oct.) 1889.

4. Üprus, Voldemar: Meningiomas multiplex cerebri, *Folia neuropath. estoni-ana* 12:86, 1932; abstr., *Zentralbl. f. d. ges. Neurol. u. Psychiat.* 67:44, 1933.

5. List, C. F.: Multiple Meningiome der Schädelbasis. (Zugleich ein Beitrag zur Differentialdiagnose der Kleinhirnbrückenwinkeltumoren), *Nervenarzt* 6:566 (Nov. 15) 1933.

6. von der Hütten: Beitrag zur Diagnose von Hypophysentumoren, *Ztschr. f. Laryng., Rhin., Otol.* 24:95, 1933.

headache and diminishing vision. Her condition was diagnosed as hypophyseal tumor, and she was operated on transnasally according to the Hirsch technic. She died three weeks after operation, and at necropsy twenty-five endotheliomas, situated chiefly at the base of the skull, were found. Frazier and Alpers<sup>7</sup> recently stated that they found only one example of multiple tumors in their series of seventy-five cerebral fibroblastomas.

Cushing<sup>8</sup> collected reports of thirteen cases from the literature and noted the frequent occurrence of multiple meningiomas with tumors of the acoustic nerve and multiple neurofibromatosis. He was of the opinion

*Review of the Literature and Report of Twenty-Two Cases of Multiple Meningiomas*

Case	Reported by	Age, Years	Sex	Number of Primary Meningeal Tumors	Associated Findings
1	Wishart.....	21	M	Numerous	Bilateral acoustic tumors and multiple neurofibromatosis
2	".....	32	F	Numerous	Unilateral acoustic tumor
3	".....	26	M	Numerous	Bilateral acoustic tumor
4	".....	77	M	Two	None
5	Schmidt.....	88	M	Two	None
6	Fraenkel and Hunt..	42	M	More than 100	Bilateral acoustic tumors
7	Westphal.....	26	F	Numerous	Bilateral acoustic tumors and multiple neurofibromatosis
8	Verocay.....	31	M	Numerous	Bilateral acoustic tumors and multiple neurofibromatosis
9	Henschen.....	25	M	Numerous	None
10	Leischner.....	40	M	Numerous	Unilateral acoustic tumor
11	Heuer and Dandy....	..*	M	Two	None
12	Greenfield.....	31	M	Three	None
13	Symonds.....	27	M	Numerous	Bilateral acoustic tumors and multiple neurofibromatosis
14	Krivy.....	..†	F	Three	None
15	Firket.....	27	F	Ten	Bilateral acoustic tumors and one spinal meningioma
16	Casper.....	..†	F	Numerous	None
17	Casper.....	52	M	Numerous	None
18	Casper.....	72	F	Numerous	None
19	Savy and others....	39	M	Two	None
20	Regnier and others..	36	M	Two	Bilateral acoustic tumors and multiple neurofibromatosis
21	Flick.....	54	F	Numerous	None
22	Hosoi.....	30	F	Thirty-eight	Multiple angiomas

\* The patient in this case was an adult.

† The patients in these cases were old.

that while these might be correlated lesions, they were of utterly different pathologic character.

Hosoi noted that in 50 per cent of the series of cases which he collected multiple meningiomas were not associated with other tumors. This suggested to him that the association of meningeal tumors and multiple neurofibromatosis was an expression of the predisposition of the person to hereditary and dysontogenetic influences.

7. Frazier, C. H., and Alpers, B. J.: Meningeal Fibroblastomas of the Cerebrum: Clinicopathologic Analysis of Seventy-Five Cases, *Arch. Neurol. & Psychiat.* **21**:935 (May) 1933.

8. Cushing, H. W.: Tumors of the Nervus Acusticus and the Syndrome of Cerebellopontile Angle, Philadelphia, W. B. Saunders Company, 1917.

More recently, Penfield and Young<sup>9</sup> reported the postmortem examination of a patient with multiple tumors in the connective tissue sheaths of nerves, in the meninges and in the central nervous system. The nature of the tumors in each situation was peculiar to the tissue in which they appeared. In addition to the neoplasms, the authors found in each of the three tissues definite evidence of a hyperplastic reaction of the cells peculiar to those tissues. They suggested that a congenital defect in the nervous system is perhaps capable of producing irritation and that this irritation causes hyperplasia of the cells which is followed by a neoplastic change. They were of the opinion that the fact that the cells of the tumors were peculiar to the tissue in which they were found speaks in favor of the production of tumor by an irritative process rather than from embryologic rests.

Much less common than reports of cases of multiple meningiomas are instances of the successful removal of these multiple tumors. Heuer and Dandy,<sup>10</sup> in 1916, reported such a case. The patient had been operated on elsewhere in 1908, at which time a single dural endothelioma, lying in the motor area, was removed. The symptoms recurred, and in 1909 another operation was performed at the Johns Hopkins Hospital; a recurrent tumor was found at the site of the previous operation and a second tumor compressed the motor speech area. A search of the literature reveals this to be the only report extant of the removal of multiple meningiomas at operation; reports of all other cases of multiple tumors were based on observations at necropsy.

The following case, in which three meningiomas were removed, was considered worthy of report:

#### REPORT OF CASE

A married woman, aged 46, registered at the clinic on April 18, 1934, complaining of pain in the head and in the right arm, which she had had for eight months, and of dimness of vision, which had been present for three months. In September 1930 she had been examined in the clinic, at which time it was found that she had mild hypertension; otherwise, she was in excellent physical condition. The onset of the illness for which she came to the clinic had occurred when, on reaching for a ball which had been thrown, she suddenly experienced a sharp pain in the right side of the thorax. Later an aching pain in the right arm developed, which was projected up to the neck and occiput and over the vertex to the frontal region. At times the pain became so severe that it was necessary to give morphine hypodermically for relief. For three months prior to her admission vision had diminished progressively, and for six weeks ataxia had been developing. She had experienced some dizziness but had had no convulsions or vomiting. Just before admission she had become conscious of weakness in the fingers of her right

9. Penfield, W., and Young, A. W.: The Nature of von Recklinghausen's Disease and the Tumors Associated With It, *Arch. Neurol. & Psychiat.* **23**:320 (Feb.) 1930.

10. Heuer, G. J., and Dandy, W. E.: A Report of Twenty Cases of Brain Tumor, *Bull. Johns Hopkins Hosp.* **27**:224 (Aug.) 1916.

hand. According to her friends, there had been a definite change in personality; at times her mind had seemed flighty and her memory poor.

General examination showed the patient to be slightly obese but in good general condition. Neurologic examination disclosed that she was slightly deaf in each ear. The corneal reflex was diminished bilaterally. The muscles of the right forearm and hand were weaker than the corresponding muscles of the left upper extremity. The Hoffman reflex was present on the right, as were moderate astereognosis and incoordination.

On examination of the eyes, the fields were normal except for enlarged blind-spots. Vision in the left eye was 6/10; in the right eye, 6/20. There were bilateral choked disks of 4 diopters, with a few hemorrhages.

The results of urinalysis and of all examinations of the blood were normal. Roentgenograms of the head gave evidence of a rounded, calcified mass in the left basofrontal region, the shape of which suggested a calcified meningioma (fig. 1).



Fig. 1.—Calcified meningioma in the left basofrontal region.

Because of the change in personality, the weakness and incoordination of the right arm, the numbness of the fingers of the right hand, the bilateral choked disks and the roentgenographic finding of a calcified mass in the left basofrontal region, a diagnosis was made of calcified tumor involving the left frontoparietal lobes. It was thought that this tumor probably was a left basofrontal meningioma.

Left transfrontal craniotomy was performed; the opening was made larger than usual because of the questionable nature of the calcified mass. As soon as the dura had been exposed, a meningeal tumor was found compressing the posterior part of the inferior frontal convolution. The tumor was firm and corresponded to the shadow found in the roentgenogram of the head. It was easily rolled from its bed and was found to measure 3 by 2 by 2.5 cm. It was removed with its dural attachment, and when the dura was incised forward a small meningioma, measuring 1 by 1 by 0.5 cm., was found and removed (fig. 2). In view of the fact that these two tumors failed to explain the weakness of the right arm and the high degree of papilledema, further search was made, and another meningioma, which measured 5 by 5 by 3 cm., was found compressing the motor cortex near the arm area. This was removed with a great deal of difficulty on account

of the vascularity of the capsule and the numerous vascular attachments. Although the situation and size of the third meningioma that was removed accounted satisfactorily for the symptoms, the basifrontal region was explored by elevating the left frontal lobe; no evidence of tumor was found. The wound was closed after the cortex had been protected with Cargile's membrane to take the place of the defects in the dura caused by removal of the attachments of the meningiomas.

Pathologically the tumors were all meningiomas, but they varied greatly in gross, as well as in microscopic, appearance. The smallest of them was very soft and friable and contained no calcium. The medium-sized tumor was hard and unyielding because of marked calcification, which had been demonstrated in the roentgenograms. The largest tumor, and the last to be removed, was well encapsulated, contained no calcium and was quite vascular (fig. 3). Microscopically

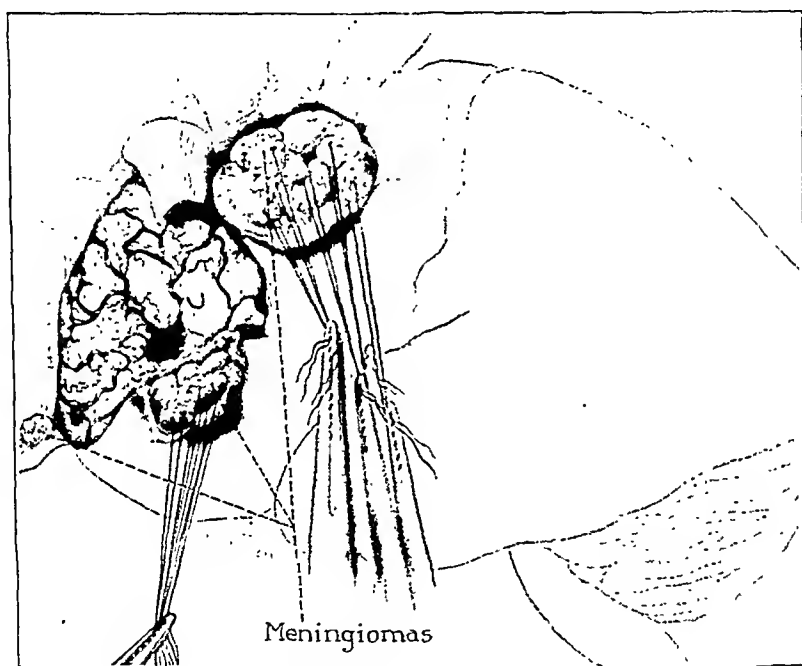


Fig. 2.—The three tumors as they appeared at operation.

it proved to belong, as did the other two, to the meningiomatous group of tumors known as meningiomas, meningeal fibroblastomas or dural endotheliomas.

At the operating table it was difficult to understand why the patient did not have aphasia, in view of the fact that the calcified meningioma compressed Broca's area. Consequently, we were not surprised that the patient became completely aphasic on the second day after the operation and remained so until the sixth day, when she began to improve. Her convalescence was otherwise uneventful. She was dismissed from the hospital on the twelfth day after operation and was allowed to return home on the fifteenth day. At the time of dismissal the papilledema was definitely subsiding, and she had completely recovered from aphasia; there was still, however, some weakness of her right arm (fig. 4).

A letter received from the patient seven months after the operation was written with her right hand, the function of which had been completely restored. She



stated that her general condition was excellent and that her vision was progressively improving.

#### COMMENT AND SUMMARY

Removal of multiple meningiomas by operation with relief of symptoms is of such rare occurrence that it warrants comment. A review of the literature fails to reveal a similar case, although multiple meningiomas have been reported from observations at necropsy and are

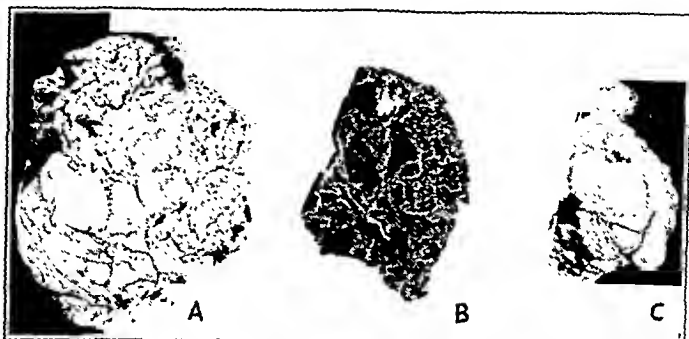


Fig. 3.—Gross specimens of the meningiomas that were removed. The measurements were as follows: *A*, 5 by 5 by 3 cm.; *B*, 1 by 1 by 0.5 cm. (including a piece of the dural attachment), and *C*, 3 by 2 by 2.5 cm.

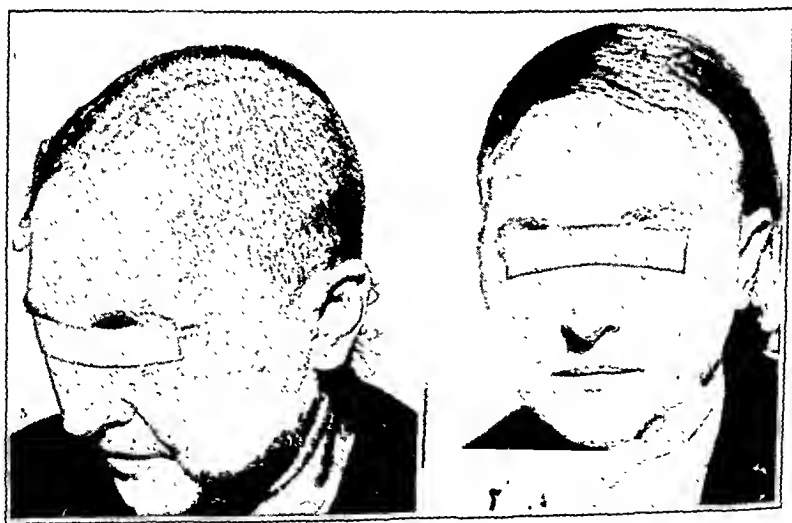


Fig. 4.—The patient sixteen days after operation, showing the well healed incision.

frequently associated with acoustic neuromas or generalized neurofibromatosis. The present case illustrates the difficulty in localizing and determining the pathologic nature of an intracranial lesion prior to surgical exposure. At operation a calcified lesion was found to correspond with the shadow in the roentgenogram, but it was felt that the presence of this tumor did not explain the papilledema or the weakness in the right hand. Further search revealed another tumor, which was responsible for these symptoms.

## ACUTE ABDOMINAL PAIN IN SICKLE CELL ANEMIA

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Attacks of acute abdominal pain with fever, muscle spasm and leukocytosis occur not infrequently with sickle cell anemia. The attacks are often severe and may be associated with signs and symptoms strongly suggesting various acute abdominal diseases. In fact, the picture may so closely simulate such a condition as to be almost indistinguishable, even if the patient is known to have sickle cell anemia. Furthermore, persons with sickle cell anemia are just as subject to the other abdominal diseases as any one else, and instances of cholelithiasis, appendicitis and other emergency conditions are well known. Hence, it is important for a surgeon to be familiar with the painful manifestations of sickle cell anemia. It is to enumerate the symptoms and signs most commonly found in this interesting phase of the disease and to report six cases in which the abdominal manifestations were outstanding that this paper is written.

*General Description.*—(Cook and Meyer [1915]; Josephs, [1928]; Sydenstricker [1920, 1929]; Eastland and Higgins [1930]).—Sickle cell anemia is of the familial hemolytic group (Sydenstricker [1924]) and occurs solely in Negroes<sup>1</sup> or in persons with Negro blood. It is characterized by the peculiar sickle or oat shape which the erythrocytes assume in a fresh preparation. The disease occurs in an active and a latent form (Sydenstricker [1924]; Huck [1923]), and one may succeed the other (Mulherin and Houseal [1924]). In the active phase there may be long periods when the hemolytic process is quiescent, and no signs or symptoms of the disease are present. The sickling trait persists throughout life. Some persons may never have the active form and hence have no anemia or any symptoms of the disease, and the anemia may be discovered only by the study of a preparation of fresh blood. It has been estimated that from 2 to 7.5 per cent (Branbau [1932]; Cooley and Lee [1926]; Sydenstricker [1920]; Miyamoto and Korb [1927]) of the entire Negro population has sickle cell anemia in the latent form, while a much smaller proportion has the active variety.

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1. The possible exceptions to this are the cases described in the reports by Stewart (1927), Archibald (1926), Lawrence (1927), Rosenfeld and Pincus (1932) and Auer (1933).

Patients with active sickle cell anemia usually complain of weakness, dyspnea and general poor health. The symptoms sometimes appear in attacks of a few days' or even months' duration and sometimes are constantly present over longer periods. At intervals the symptoms disappear entirely. There is a tendency for the patient to contract an intercurrent infectious disease. Often there is a history of attacks of malaise, fatigability, fever and jaundice, sometimes associated with abdominal pain and vomiting, sometimes with pain in the joints and long bones. Several instances have been reported in which laparotomy (Levy [1929] and cases 1, 2 and 6 in this paper) or operation for acute osteomyelitis (Dreyfoos [1926]; Alden [1927]; Leivy and Schnabel [1932]) has been carried out with negative results and subsequent discovery of sickle cell anemia. Bronchitis is rather common, and night sweats are not infrequent.

On physical examination one often finds some enlargement of the heart with a systolic apical murmur, moderate general glandular enlargement and a palpable liver. It is probable that in the active form in young children the spleen enlarges until the age of from 3 to 5 years and then gradually becomes smaller (Anderson and Ware [1932]; Ching and Diggs [1933]; Stewart [1927]). In cases of the latent type no gross evidence of splenic changes may be observed at autopsy. In some clinics ulcers of the leg have been reported in many cases, though that has not been my experience. Infantile genitalia have been noted in some of the malnourished patients. Characteristic radial striations in the calvarium are sometimes seen in roentgenograms (Cooley and Lee [1925]; Moore [1929]).

*Hematology of the Active Form.*—Anemia is usually present. In 49 instances Anderson and Ware (1932) found an average red blood cell count of 3,500,000, a hemoglobin content between 30 and 40 per cent and a leukocyte count of from 10,000 to 12,000. The erythrocyte count may be as low as 600,000 and the hemoglobin content as low as 10 or 12 per cent, while the white blood cell count has been reported in some cases to be above 60,000. During exacerbations in younger persons lymphocytosis is not uncommon (Landon and Lyman [1929]; Bothe [1933]; Hamilton [1926]; Russell and Taylor [1932]). The color index has been reported as from 0.7 to 1.4. Varying degrees of anisocytosis and poikilocytosis are found. In the active phase the erythrocytes assume the sickle shape almost immediately in the preparation of fresh blood. The sickling varies greatly, even in the same patient, in the time when it appears, in the percentage and in the subsequent return of the red blood cells to normal shape (Cooley and Lee [1925]). No relation between the degree of sickling and the severity of the symptoms has been noted. Nucleated red blood cells

and reticulocytes are present in varying percentages. The changes in the platelets are not noteworthy. Hyperbilirubinemia with mild jaundice and increased urobilin in the urine is common. The van den Bergh reaction is usually negative in the direct phase and positive in the indirect. The fragility of the red blood cells is not increased, and it may be slightly diminished. The urine may have low specific gravity.

*Pathologic Changes.*—The changes most characteristic of this anemia are to be found in the spleen, both in the latent and in the active phase. As described by Rich (1928), they "consist in a congenital malformation of the sinuses of the spleen, which permits the free escape of blood into the pulp." As in congenital hemolytic jaundice, the entire pulp may be filled with blood. "The anomaly characteristic of sickle cell anemia is the pronounced malformation of the sinuses immediately about the malpighian bodies, leading to the formation of pools of blood partially or completely surrounding" these structures and probably caused by imperfections in the ampullae of Thoma. There may be "an abnormal development of capillaries" throughout the malpighian body. "The reticulum of the spleen is not primarily abnormal." Hemosiderin may be demonstrated in the tissues (Graham [1924]; Rich [1928]). The bone marrow is hyperplastic in the active stage.

I am reporting six cases of sickle cell anemia because of the abdominal manifestations.

#### REPORT OF CASES

*CASE 1.*—*Priapism four months previously. Epigastric pain, constipation, vomiting, malaise, jaundice, marked distention and leukocytosis. Similar attack three months previously. Diagnosis, probable ileus. Exploratory laparotomy with normal findings. Sickle cell anemia discovered subsequently.*

Winston R., a 14 year old Negro, was admitted to the hospital on Aug. 20, 1932, with a complaint of abdominal pain, obstipation, malaise and jaundice. The attack began about seven days previously, when the jaundice was first noticed and when the constipation commenced. The abdominal pain had varied in degree, had sometimes been severe and had always been located in the epigastrium. The patient had vomited on two or three occasions but had not done so for the past three days. Various cathartics had been taken without effect. It was interesting to note that he had a similar attack of pain, jaundice and constipation three months before, and his mother added that on a number of occasions during the past five years he had "spells" of jaundice lasting for a few days or a few weeks, during which time he would feel badly. Four months previous to examination he had been treated successfully for priapism in the urological dispensary by aspiration of blood clots from the corpus cavernosum.

On examination the temperature was 99.6 F., the pulse rate was 80, the respiratory rate was 18 and the white blood cell count was 30,000. The patient was definitely jaundiced, the skin was dry, there was slight general glandular enlargement and the heart and lungs were normal. The abdomen was markedly distended and rather tense. There was very slight generalized tenderness, perhaps more in the epigastrium and in the right upper quadrant, but there was no

definite muscle spasm. The liver and the spleen were not palpable, nor was any other mass felt. There was no rebound tenderness, and no peristalsis could be seen. An enema was ineffectual, and gastric lavage yielded about 150 cc. of bile-colored fluid.

The etiology of a probable ileus was not clear, and after observing the patient for some hours a laparotomy with appendectomy was done by Dr. H. J. Warthen Jr. The findings were normal throughout. The temperature rose to 101 F., and the pulse rate the day after the operation was as high as 180 and did not fall below 120 for forty-eight hours. The van den Bergh test showed a prompt biphasic reaction and 8 mg. per hundred cubic centimeters. The white blood cell count the next day was 42,000, and it was only then that a fresh blood smear was found to show sickle cells.

The patient was transferred to the medical service, where he remained for about seven weeks. The hemoglobin content was 40 per cent, the red cell count, 2,800,000, polymorphonuclears, 91 per cent, and lymphocytes, 8 per cent. On the second day postoperatively the enemas began to be effectual, and the distention was gradually relieved. The nonprotein nitrogen content was elevated, being 80 mg. on the third postoperative day and 50 mg. on the fifth day. The cholesterol content was 166 mg. per hundred cubic centimeters. The red blood cell count fell to 1,500,000 by the sixth day, and the patient was given a transfusion of blood. On the same day the value for nonprotein nitrogen fell to 32 mg. per hundred cubic centimeters, or normal. It was then found that the liver was palpable 3 fingerbreadths below the costal margin. The spleen and kidneys were not palpable. The hemoglobin content rose to 40 per cent and the red cell count to 2,100,000 after the transfusion. The white cell count was then 16,600. On the eighth day the patient had a good deal of abdominal pain, which was relieved by enemas, and he vomited once. The wound was now healed, and on the twelfth postoperative day the hemoglobin content was up to 45 per cent, the red cell count to 2,500,000 and the reticulocyte count 1.1 per cent. The patient improved slowly and gradually gained weight. The white cell count remained elevated at about 20,000. The nonprotein nitrogen content did not rise again during his stay in the hospital. The gastric analysis with histamine showed free acid of 22 mg. and a combined acid of 20 mg. No ulcers of the leg were present, nor was there any evidence of cardiac enlargement.

The patient was followed in the dispensary from October 13 to July 7, 1933, at which time he was admitted to the hospital because of weakness and cough. His temperature was 101.6 F., and there were jaundice, pallor and signs of bronchopneumonia at the base of each lung. The red cell count was 1,200,000, and on two occasions transfusions of 300 cc. each were given, bringing the red cell count up to 2,400,000. The fever subsided, and the patient was allowed to go home after two weeks in the hospital, feeling much better.

He was readmitted on November 7 for a transfusion of blood. The hemoglobin content was 40 per cent, the red cell count, 1,600,000, and the white cell count, 18,200. In the interim the patient had been attending school and playing games, and had no complaint. There had been an occasional attack of abdominal pain but no constipation. It should be noted that roentgenograms of the chest indicated for the first time some changes at the base of each lung and calcified glands suggesting tuberculosis. He was jaundiced as before, the heart was slightly enlarged, and there was a systolic murmur at the apex transmitted to the axilla. The liver was greatly enlarged, and the spleen was not palpable. A series of roentgenograms of the gallbladder showed a normal condition.

Since then the patient has been seen on several occasions in the dispensary, and has gained strength, is going to school and is carrying on his usual line of activity.

*CASE 2.—Sickle cell anemia previously recognized. Generalized abdominal cramps, vomiting, slight general abdominal tenderness and distention. Temperature, 100.2 F. White blood cell count, 20,000. Pain increasing. Exploratory laparotomy. Negative findings. Pneumonia postoperatively.*

Helen W., a 10 year old Negro girl, was admitted to the hospital on Nov. 2, 1932, because of severe, generalized abdominal cramps of twelve hours' duration. She had been constipated for three days but had not vomited. Occasionally the pains seemed worse on the left side, but the patient was not sure. She was known to have sickle cell anemia and had a somewhat similar attack three years previously. Several months previously she had pain in one extremity which was thought at first to be due to acute osteomyelitis.

Physical examination revealed: temperature, 99 F.; pulse rate, 110; respiratory rate, 32, and white blood cell count, 20,000. The heart and lungs were normal. There was a subicteric tint to the scleras. The patient was writhing in pain. The abdomen was slightly distended and was held rather tense. There was moderate tenderness over the abdomen, but no real muscle spasm or localized pain was noted. The liver and spleen were not palpable.

It was believed that this was probably a manifestation of the sickle cell anemia or possibly central pneumonia; so the patient was observed for nine hours. During that time the pain increased in frequency and severity and she began to vomit. An enema was not effective. She kept her thighs flexed constantly. The temperature rose to 100.2 F. Since it seemed possible that appendicitis or early ileus was present, an exploratory laparotomy was done by Dr. I. Ridgeway Trimble. No abnormality could be found. The appendix was removed and was normal. Convalescence was stormy, owing principally to pneumonia at the base of each lung. The abdominal pain subsided on the third postoperative day. The leukocyte count remained high for several days, and on the sixth postoperative day rose to 46,000. The hemoglobin content was 76 per cent at first but dropped to 42 per cent on the tenth postoperative day, the red blood cell count at that time being 1,800,000 and the white blood cell count, 58,000 with 79 per cent polymorphonuclear leukocytes. Marked sickling was present. There was slight albuminuria, the tuberculin and Wassermann reactions were negative, and a blood culture was sterile. The pneumonia began to resolve rapidly by the fifteenth postoperative day, and the patient was soon much improved.

Since then she has been followed in the dispensary. On one occasion she had an attack of mild pain in the upper portion of the abdomen and constipation which lasted for four days and was not relieved by enemas. The temperature was normal and the white blood cell count was 20,000. There was diffuse tenderness in the upper portion of the abdomen but no muscle spasm. Since then she has had no abdominal pain.

*CASE 3.—Abdominal pain, nausea and constipation. Known to have sickle cell anemia. Temperature, 98 to 100.2 F. Tenderness and muscle spasm in the hypochondrium on the right and at McBurney's point. No jaundice. White blood cell count, 20,000; hemoglobin, 50 per cent. Appendicitis and cholecystitis simulated. Gradual disappearance of pain.*

Eugene A., a 14 year old Negro, was admitted to the Harriet Lane Home for the fourth time with the complaint of abdominal pain of eighteen or twenty hours' duration. He had been nauseated but had not vomited or had diarrhea.

There had been no bowel movement for two or three days. On the previous evening he complained of slight pain in the left side of his chest. His mother said that he had been having attacks of abdominal pain every few weeks and that he tired easily and had dyspnea on exertion.

The past history was of interest in that the patient had been admitted on three previous occasions, on the first of which sickling was found. From 2 to 4 years of age he had recurring attacks of abdominal pain and fever, though he was not observed during any of these attacks. At that time there were noted general glandular enlargement, absence of jaundice, slight cardiac enlargement, the edge of the liver 3 fingerbreadths below the costal margin and an otherwise normal abdomen. The white blood cell count was 15,000, 24 per cent being polymorphonuclears, 3.5 per cent eosinophils, 7.5 per cent neutrophilic myelocytes and 48 per cent lymphocytes. From the age of 7 to 13 he again had attacks of pain, "abdominal cramps" and headache, and mild jaundice was noted. There had been one attack in which he complained of cramplike pain in the abdomen, elbows and knees with numbness in the fingers and toes. He was observed again in the hospital. This time the liver was not palpable, and there was marked anemia (hemoglobin, 40 per cent; red blood cell count, 1,700,000). Roentgenograms of the skull showed thickening of the outer table, principally in the vertex, with a peculiarly granular appearance.

On examination the temperature, pulse and respiratory rate were found to be normal. The patient was well nourished and did not look very sick but had considerable abdominal pain. There was no jaundice or icteric tinge to the scleras. The heart was a little enlarged, and a systolic murmur was transmitted a short distance beyond the axillary line. The abdomen was not distended but rounded and moved only fairly well on respiration. There were marked tenderness and muscle spasm in an area about 5 or 6 cm. in diameter just beneath the costal margin in the mammary line. No masses could be felt, and one could not be sure whether the liver was enlarged because of the muscle spasm. There was another area of about the same size at McBurney's point where there were definite tenderness and rigidity. There was rebound pain over the region of both the gallbladder and the appendix. Elsewhere, the abdomen could be palpated quite deeply without causing pain. There was a leukocyte count of 20,500, with 60 per cent polymorphonuclears and 30 per cent lymphocytes. The red blood cell count was 1,900,000, the hemoglobin content was 50 per cent, and there was marked sickling in the preparation of fresh blood (30 per cent immediately and 100 per cent in twelve hours). The urine was normal.

Although it was known that the patient had sickle cell anemia, my associates and I were aware that such a patient is just as subject to the acute abdominal diseases as other people. With such tenderness in the region of the appendix and gallbladder, together with nausea, constipation and leukocytosis, some concern was felt. With the history of previous attacks of abdominal pain it was decided to observe him a few hours. An enema was administered which proved effectual and partially relieved the pain in the right lower quadrant. Eight hours later the tenderness and muscle spasm had disappeared, and although tenderness and muscle spasm remained in the right upper quadrant there was no spontaneous pain. Gradually over a period of four or five days the signs and symptoms at the right costal margin disappeared. Very slight icterus appeared which subsided in a few days. A month later the patient again complained of abdominal pain which was generalized but most annoying on the right side. There was slight tenderness over the edge of the liver, which could just be palpated. The white blood cell count was 19,000; the hemoglobin content was 42 per cent, and sickling was

active. Urobilin was present in the urine in a large amount. The urine was not remarkable except for a persistently low specific gravity (from 1.008 to 1.002). The patient has had no complaint during the past six months.

It is interesting to note the similarity in the abdominal findings in this case and in that of Smith (1928). In each there were separate and distinct areas of tenderness and muscle spasm over the gallbladder and the appendix.

*CASE 4.—Sickle cell anemia and priapism. Attacks of epigastric and hypochondric pain on the right radiating to the back. Bile in stool variable in amount. Cholecystectomy for cholecystitis and cholelithiasis. Normal convalescence except for slow healing of cutaneous edges. Death one year later of circulatory failure and bronchopneumonia. Autopsy.*

On Aug. 2, 1925, Willie B., a 23 year old Negro, was admitted to the urological service with priapism. This condition was successfully treated by aspiration of blood clots from the corpus cavernosum. The patient was found to have active sickle cell anemia and was then transferred to the medical service. He was well developed and well nourished. There were jaundice and general glandular enlargement. The heart was a little enlarged, and a systolic murmur was audible at the apex. There were moderate tenderness and muscle spasm in the hypochondrium on the right side. The results of the abdominal examination otherwise were not remarkable; the spleen was not palpable. During the next six weeks his temperature varied from 99.4 to 103 F. The red blood cell count was 2,200,000; the hemoglobin content, 60 per cent, and the color index, 1.36. The white blood cell count varied from 13,700 to 45,000, with a normal distribution of cell types. There was some albuminuria. Roentgenograms of the gallbladder showed numerous stones. On several occasions tenderness over the gallbladder was noted, though the patient complained of very little spontaneous pain during his stay.

He was at home for the following year and continued to have poor health. He had pneumonia with increased jaundice lasting for about a month. Headache, night sweats and loss of weight were the outstanding symptoms for several weeks previous to the next admission. He fainted once. For a period of two weeks he had pains in the knees, shoulders and elbows. There were two attacks of epigastric pain radiating through to the spine, the attacks being followed for a short time by clay-colored stools.

On examination he was found to be deeply jaundiced and very pale, but still moderately well nourished and in no great discomfort. The findings were roughly as before save for more marked tenderness and muscle spasm in the right upper quadrant of the abdomen. The temperature was normal. The blood showed, as before, marked sickling. The red blood cell count was 2,100,000; the hemoglobin content was 54 per cent, and the color index was 1.1. The white blood cell count varied from 12,000 to 18,000. A cholecystectomy was performed on June 25, 1928, by Dr. Deryl Hart, who found a thickened gallbladder filled with many stones. There were no stones in the common duct, which appeared normal in every respect. Convalescence was uneventful save for very slow healing of the cutaneous edges. The patient was discharged considerably improved five weeks after the operation. The van den Bergh reaction was 7.9 mg. per hundred cubic centimeters (direct) as compared with 24.8 mg. (direct) on admission to the hospital.

On April 24, 1929, the patient was admitted to the Baltimore City Hospital to the service of Dr. Thomas R. Boggs, with edema of the feet, ankles and face of five days' duration. Chills, fever and night sweats with anorexia and weakness were complained of. He presented signs of circulatory decompensation, bronchopneumonia and some nephritis. Jaundice and general glandular enlargement were noted as before. The heart was moderately enlarged and the pulse was collapsing.



There was some tympanites with resistance to palpation in the hypochondrium on the right. Albuminuria and cylindruria were marked. The phenolsulphon-phthalein test showed only 15 per cent excreted in the first hour. The nonprotein nitrogen content was 125 mg. per hundred cubic centimeters. Death followed in a short time.

Autopsy revealed changes typical of sickle cell anemia in the spleen, hyperplastic bone marrow, cardiac hypertrophy and dilatation, pulmonary edema, bronchopneumonia and congestion of the kidneys with scarring, but little evidence otherwise of nephritis. The liver was normal except for jaundice.

*CASE 5.—Cramplike pains in the lower portion of the abdomen following diarrhea and vomiting simulating acute digestive disturbance. Diarrhea followed by constipation. Subsequent localization of pain in the hypochondrium on the right side. Mild jaundice. Sickle cell anemia demonstrated. White blood cell count, 18,000. Gradual subsidence of pain. Gallbladder not demonstrated by Graham test. Diagnosis: sickle cell anemia with probable cholecystitis.*

On March 21, 1933, Edward B., a 38 year old Negro, was admitted to the hospital because of diarrhea and vomiting of three days' duration and severe cramplike abdominal pain in the previous twenty-four hours. His past history was interesting in that he had noticed weakness in his legs, pain in the joints, constipation and headache. He had lost 25 pounds (11.3 Kg.) in the previous year. There had been no previous attack similar to the present one. He had gonorrhea a few years previously.

The temperature was 102 F., the pulse was 88, the respiratory rate was 26, and the blood pressure was 130 systolic and 80 diastolic. The patient was well developed, did not look ill and was in no great discomfort. The scleras were mildly jaundiced. The general physical examination revealed no abnormality save tenderness and slight rigidity in the hypochondrium on the right side. There was some induration about the prostate. The red blood cell count was 5,800,000; the hemoglobin content was 106 per cent, and the white blood cell count was 18,500 with 81 per cent polymorphonuclears. A preparation of fresh blood showed marked sickling of the erythrocytes. The ven den Bergh reaction was a delayed biphasic response equivalent to 4.7 mg. per hundred cubic centimeters. There was bile but no occult blood or parasites in the stool. The urine contained a few white blood cells, and for the first two weeks urobilin was present. Both eventually disappeared.

On the day of admission the patient vomited several times and became constipated. These symptoms disappeared on the second day, and thereafter he had no complaints during the subsequent month of hospitalization. The tenderness in the right upper quadrant persisted for several days and gradually subsided. The temperature remained at about 101 F. for the first few days and then gradually fell to normal during the following week. The white blood cell count remained at 18,000 for forty-eight hours, then fell to 9,000 on the third and the fourth days, and thereafter was between 4,000 and 5,000, with a normal distribution of cells. There was no increase of fragility of the red blood cells. The red blood cell count and the hemoglobin content remained high. Visualization of the gallbladder was not possible, even after intravenous administration of the dye, and no stones were seen in the roentgenogram.

It was thought that the patient probably had chronic cholecystitis in addition to the sickle cell anemia and low grade prostatitis. He has been well ever since. An operation was not permitted.

CASE 6.—*Generalized cramplike abdominal pain, nausea, mild fever, leukocytosis, boardlike abdominal rigidity and tenderness. Exploratory laparotomy with normal findings. Uneventful convalescence.*

Samuel S., a 36 year old Negro, was admitted to the hospital on Aug. 12, 1934, because of increasingly severe, generalized, cramplike abdominal pain with which he had wakened twelve hours earlier. He said that when the pain became extreme it felt as though it extended into both thighs anteriorly. He had taken a cathartic at once, which was followed two hours later by a bowel movement without relief of symptoms. He had been nauseated but had not vomited. There was no history of previous indigestion, abdominal pain or jaundice.

His past history was interesting in that he had an attack of severe abdominal pain in 1929, after which he was treated with ice-pack for what was termed appendicitis. Three months subsequently he was operated on in another hospital for what he was told was a ruptured appendix, and the abdomen was drained. In 1932 he returned to the same hospital with severe abdominal pains, and the abdomen was explored a second time. He did not know what the findings were but asserted that his convalescence was uneventful and that he had been symptom-free since that time. He had "rheumatic" pains in the knees and joints from the age of 12 to 23. These would be present for a day or even a week and then subside, with varying intervals of freedom followed by a recurrence in some other joint, such as the elbow or shoulder. There was never redness, swelling or tenderness of the joints. During the past two or three years he had occasional mild pain in the joints without fever and without having been incapacitated. He was never sickly as a child or as an adult, nor had members of his family been considered weak or delicate. He worked regularly as a laborer, and except for the aforementioned episodes had been perfectly well. He had gonorrhea five years previous to admission to the hospital.

On examination the temperature was 99.4 F.; the pulse rate, 100; the respiratory rate, 26 to 30, the blood pressure, 165 systolic and 110 diastolic, and the urine, normal. The patient was a strong, robust looking Negro who complained bitterly of severe abdominal pain. He looked sick. His thighs were flexed, and he guarded his abdomen carefully. His color was good, and he had no cough, but the alae nasi dilated with each inspiration. There was no jaundice and no general glandular enlargement. Examination of the heart and lungs gave negative results. The white blood cell count was 13,000, and the hemoglobin content was 90 per cent.

The abdomen was symmetrical and slightly distended and moved very little on respiration. There were an old, well healed low right rectus incision, and a drainage stab wound in the right flank, neither of which was tender or contained a hernia. Generalized tenderness and boardlike rigidity were present over the entire abdomen, perhaps a little more pronounced in the region about the umbilicus, but at no point could one palpate deeply. Hepatic dullness was present. The pain seemed to be constant. It was my impression that he had peritonitis, possibly from a perforated ulcer, and a laparotomy was advised and performed. There was no peritonitis and no free fluid, and the stomach and intestine everywhere appeared normal. A few omental adhesions about the old incision were present. The gallbladder was thin-walled, soft, contained no stones and could be emptied on pressure. The liver was normal in size and consistency. The pancreas was normal. It was then found that the spleen was enlarged to about twice its normal size. It was firm, nodular and adherent to the diaphragm. We then suspected that this was a case of sickle cell anemia, and a smear of fresh blood showed immediate sickling of the red blood cells. The patient's convalescence was uneventful.

Further study revealed that the hemoglobin content was 90 per cent or more and that the red blood cell count was 4,000,000. The sedimentation rate was 15 mm. per hour, and the icterus index was 11. The van den Bergh reaction showed an "indirect trace." The leukocytosis disappeared in a few days. The hemoglobin content remained high, and the urine remained normal except for a low fixed specific gravity by the Mosenthal test. The variation in specific gravity was from 1.009 to 1.014.

This case was particularly interesting, not only because of the boardlike rigidity of the abdomen and the picture of severe peritoneal irritation but also because of the lack of jaundice and the general good health.

#### ABDOMINAL MANIFESTATIONS

Many patients with the active form of the disease have at some time attacks of acute abdominal pain, fever, mild jaundice and leukocytosis. The pain may be in the left upper quadrant, suggesting splenic infarcts, or in the epigastrium and right upper quadrant, simulating cholecystitis or hepatic tenderness from other causes or even gastric or duodenal disease. Again, there may be a cramplike pain, either generalized or localized in the epigastrium, associated with nausea, vomiting, obstipation and distention and strongly suggesting intestinal obstruction. Instances are known in which acute appendicitis has been mimicked, and on occasions acute salpingitis has been erroneously diagnosed. The symptoms and signs may vary in the same person from day to day, so that more than one abdominal condition is portrayed.

Perhaps the most common type of pain is that which occurred in the first case reported (Herrick [1910]). The patient described these episodes as "bilious attacks" with severe epigastric pain, vomiting, slight jaundice and, later, dark urine. The duration may be from a few hours to several days. The jaundice is not of the obstructive type. Often there is some muscle spasm (Mason [1922]), particularly tenderness over a palpable edge of the liver; the temperature may range up to 102 or 103 F., and the white blood cell count, though usually from 15,000 to 20,000, may be over 60,000. It is possible to have an attack at a time when there is no jaundice (Huck [1923], cases 1 and 2). Epigastric pain and pain in the left upper quadrant (Sydenstricker, Mulherin and Houseal [1923]; Anderson [1926]) sometimes coming on after meals may strongly suggest the presence of a gastric ulcer. On the other hand, pains in the hypochondrium on the right side are not infrequently due to actual cholecystitis and cholelithiasis. Washburn (1911) and Hamilton (1926) have reported such instances, and of the six patients whose cases are reported here, one (case 4) was proved to have gallstones and another (case 5) probably had them.

In another group the condition clearly simulates appendicitis, for example, in cases of J. Levy (1929, first reference), Leivy and Schnabel (1932), Dreyfoos (1926), Smith (1928) and in cases 2 and 3 reported

here. There may be generalized cramplike abdominal pain, nausea, vomiting, constipation, fever and leukocytosis, with generalized tenderness or pain and rebound tenderness in the right lower quadrant. Jaundice is not necessarily present at first, and neither the liver nor the spleen may be palpable. In case 3 icterus was not noticeable at the onset, though mild jaundice developed a few days subsequent to the attack. In case 2 there was some difference of opinion at the onset as to whether or not mild jaundice was present. Each patient was observed for several hours after admission; in case 3 the symptoms lessened and the tenderness over McBurney's point almost entirely disappeared after an enema, while in case 2 the picture became more and more indicative of appendicitis, eventually leading to an exploratory operation with normal findings.

In other instances, for example in cases 1 and 6, the history of cramplike abdominal pains, vomiting and obstipation together with tympanites force one to consider intestinal obstruction. The pains may be in the lower portion of the abdomen and suggest salpingitis, as in the case reported by Ching and Diggs (1933). Again, the pain may appear in different places at various times in the same person and cause more than one diagnosis to be made (Leivy and Schnabel [1932]).

In view of these protean manifestations, it seems possible that a number of cases of unexplained pain in the abdomen or extremities in Negroes may be due to sickle cell anemia.

#### DIAGNOSIS

There are obviously two steps in the diagnosis: first, the establishment of the presence of sickle cell anemia and, second, the decision that the abdominal symptoms are or are not attributable to this disease. If this form of anemia is suspected its presence may readily be proved by the proper examination of a preparation of fresh blood.<sup>2</sup> The second problem is more difficult. If the signs and symptoms are such that the patient may be observed for some time the condition will usually improve and an operation may be obviated. On the other hand, it is to be borne in mind that a real emergency may exist, and if there is no amelioration one may be forced to explore the abdomen. In the ultimate analysis the surgeon must rely on his experience in judging abstractly whether or not an immediate exploration is indicated. A history of previous similar attacks with jaundice is most helpful in making the decision.

Leukocytosis is usually present in the abdominal crises of sickle cell anemia and is often much higher than that which would be expected of

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2. A small drop of blood is placed on a no. 1 cover-slip, and the latter is inverted on a glass slide and sealed with petrolatum.

the disease simulated. No reliance, however, can be placed on this as a diagnostic point, for abdominal crises have been reported in which there was slight leukocytosis or none.

It is well to bear in mind that jaundice due simply to uncomplicated sickle cell anemia is not obstructive, that there are hyperbilirubinemia, hyperurobilinuria and usually an indirect van den Bergh reaction and that urobilin is present in the highly colored stools. The temperature is often elevated to 101 or 102 F., and has been seen at 104 F. on several occasions. There is likely to be low gastric acidity and an absence of occult blood in the stool. Attacks of pain simulating acute osteomyelitis, acute arthritis or rheumatic fever may occur in patients who are subject to these abdominal crises.

The cause of the pain is unknown. The most widely accepted theory is that it is due to infarcts in the spleen or to the perisplenitis which is so frequently noted at autopsy. These could account for many of the symptoms, particularly the pain in the left upper quadrant and epigastrium and perhaps the tympanites. On the other hand, they do not so readily explain the pain and tenderness in the right upper quadrant and over McBurney's point or that in the lower part of the abdomen. Furthermore, in the cases of Leivy and Schnabel (1932) and of Landon and Lyman (1929) identical abdominal crises recurred after the spleen had been removed. Bothe's patient apparently continued to have similar if not such severe attacks after splenectomy. The embolus in the hepatic artery which was suggested in the case of Yater and Mollari (1931) was not proved. Thrombosis in the liver is not common. It is conceivable that the enlargement of the liver may in some way be responsible for the hypochondriac pain on the right side, but this is not likely. Certainly gallstones occur in some persons (Miyamoto and Korb [1927]; Washburn [1911]; Hamilton [1926]; Graham [1924], and case 4, reported here) and are responsible for hypochondriac pain in the right side, but there are patients with similar pain who have no cholelithiasis or cholecystitis (Hamilton [1926]). Constipation is often associated with the attacks, but no changes have been noted in the colon. It has been suggested that changes in the spinal cord or even pain from nerve roots due to bony changes in the vertebrae were responsible (Leivy and Schnabel [1927]), but this has not been established.

#### TREATMENT

There is no specific therapy for the disease or for the abdominal crises. General supportive measures, hygienic improvements and transfusions if the hemoglobin concentration is very low are customarily employed for the disease itself. For the abdominal manifestations a policy of watchful waiting with mild sedatives, heat and enemas is all

that seems advisable. Torrance and Schnabel (1931; 1932) have recommended the use of potassium sulphocyanate and have advanced an interesting theory as to the rapidity of erythrocytic clumping. Splenectomy is not recommended (Hahn and Gillespie [1927]; Stewart [1927]; Bell et al. [1927]; Hahn [1928]; Landon and Lyman [1929]; Leivy and Schnabel [1932]; Bothe [1933]).

Patients with this disease not seldom become candidates for some form of operative therapy unconnected with the anemia. It has been my experience that patients with the latent form stand such procedures as well as other people but that those patients in whom the disease is or has been in active phase may occasionally do very badly. One such patient underwent a simple hysterectomy and salpingectomy. Before operation her general condition was good and the hemoglobin content was 90 per cent, the white count was 8,500, and she stood the actual operative procedure well. Two days later there developed what was apparently a crisis of the anemia; the hemoglobin content fell rapidly, while the white blood cell count varied from 27,000 to 60,000. She was irrational and had marked tachycardia, and on the fifth postoperative day jaundice became pronounced and increased rapidly until death on the seventh postoperative day. The autopsy showed a rather large spleen characteristic of sickle cell anemia with infarcts, necrosis and adhesions. There was some midzonal necrosis of hepatic cells, with moderate pulmonary and cerebral edema. The case of the patient of Ching and Diggs (1933), who died shortly after a laparotomy, is probably another case in point.

#### SUMMARY

Attacks of acute abdominal pain occur not infrequently in sickle cell anemia. These attacks may be quite severe and may be accompanied by nonobstructive jaundice, fever, muscle spasm, leukocytosis, nausea and vomiting. The pain is usually in the upper portion of the abdomen, in the epigastrium or in the left or the right upper quadrant. It may be so situated as to simulate cholecystitis, appendicitis or salpingitis, or the picture may suggest ileus. Patients with this condition are subject to the same abdominal diseases as are other persons, so it is important for the surgeon to be familiar with this phase of sickle cell anemia. Attacks of pain in the bones or joints not unlike acute osteomyelitis or acute rheumatic fever are well known. A history of previous abdominal crises with jaundice is one of the more important points in deciding whether or not a patient has pain from sickle cell anemia or from one of the more familiar abdominal diseases.

Patients with latent sickle cell anemia usually stand operative procedures well; those with the active form present a better risk than their general condition or degree of anemia would seem to indicate.

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# CHANGES PRODUCED BY VARIOUS OPERATIONS ON THE STOMACH

SHOWN BY THE USE OF A MODIFIED ACID TEST MEAL

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Posterior gastro-enterostomy performed in properly selected cases has long been accepted as one of the most satisfactory procedures in the treatment of duodenal ulcer. Two reasons have generally been advanced in explanation of its efficacy. First, it has been stated that the formation of a gastro-enterostomy stoma allows the gastric contents to pass into the jejunum without going through the duodenum, thereby removing the irritation of acid and food and allowing the ulcer to heal. Roentgenologists have taught, however, that in most patients unless the pylorus is completely obstructed the gastric contents leave the stomach to a large degree not through the gastro-enterostomy stoma but through the pylorus; and in spite of the fact that the ulcer continues to be exposed to the irritation of gastric contents, though perhaps for not so long a time, it usually proceeds to heal. The second explanation which has been offered is that gastro-enterostomy or one of various similar operations brings about a reduction in gastric acidity by allowing the duodenal contents to regurgitate into the stomach and neutralize the acid. The evidence in favor of this theory which has been obtained by the use of a test meal of the Ewald type is not entirely satisfactory. The reduction in acidity as found by most observers is small in amount and not always demonstrable.

Thus, Wilensky and Crohn<sup>1</sup> studied patients from one to four years after posterior gastro-enterostomy, posterior gastro-enterostomy with exclusion of the pylorus, pylorotomy or partial gastrectomy had been performed and found only a slight decrease in acidity. Lewisohn and Feldman<sup>2</sup> found that the acidity was reduced in nine of twelve cases of posterior gastro-enterostomy and in twenty-eight of fifty cases of

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gastro-enterostomy with pyloric exclusion (Berg's method) in which the patient was examined from three to five years after the operation. In eight of the same series the acidity was higher than before operation. Lewisohn<sup>3</sup> concluded after a study of ninety-two cases of gastro-enterostomy with or without pyloric exclusion that after a lapse of many years the acidity was practically unchanged, and he advised a more radical procedure for the treatment of peptic ulcer.

More striking evidence of definite change produced by gastro-enterostomy is obtained when an acid meal consisting of from 100 to 300 cc. of from 0.3 to 0.5 per cent hydrochloric acid is substituted for the Ewald type of meal. The use of an acid meal furnishes an index of another factor, the ability of the stomach to reduce excess acidity. Olch<sup>4</sup> administered an acid meal to a series of dogs before and after gastro-enterostomy, a Finney pyloroplasty or a Polya resection and found that these operations resulted in a more rapid reduction in the strength of the acid, the efficiency of the procedures in producing this reduction being in the order given. Elman and Rowlette<sup>5</sup> performed a modified Rammstedt operation on dogs and found increased neutralization of the acid test meal and also an increase in the emptying time of the stomach. Elman<sup>6</sup> also gave the acid meal to patients before and after gastro-enterostomy and found that the operation increased the amount of reduction of the acid. It is of interest that he noted in studying patients with duodenal ulcer and some patients with a certain amount of pyloric obstruction that before operation there was a diminished ability of the stomach to reduce the acidity of the meal.

Since we<sup>7</sup> have shown that the reduction which occurs in the acidity of an acid test meal introduced into the intact stomach is due mainly to dilution and not to neutralization, it seemed of value to investigate further the nature and importance of this phenomenon after various operative procedures used in the treatment of duodenal ulcer had been performed.

#### METHODS

The acid meal that we used consisted of 300 cc. of approximately tenth-normal hydrochloric acid in which was dissolved a small amount of the sodium salt of phenolsulphonphthalein. The phenolsulphonphthalein becomes red when alkalized, and changes in its concentration can be accurately determined by means of a colorimeter, with an alkalized portion of the original solution

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used as a standard. We have found that if 12 mg. of the sodium salt of phenolsulphonphthalein is added to 1,100 cc. of the acid solution the color resulting when a portion of it is alkalinized will be most satisfactory for colorimetric determinations.

All the experiments were performed on healthy dogs which had been fasting for approximately twenty-four hours. Before the acid meal was introduced the contents of the stomach were aspirated, and the stomach was thoroughly lavaged with a portion of the acid solution of phenolsulphonphthalein. The acid meal was then introduced by a stomach tube, and 1 mg. of histamine was administered intramuscularly. We used histamine in all the experiments in order to reproduce as much as possible the conditions in a secreting stomach. At the end of one-half hour the acid meal was removed from the stomach and another 300 cc. of the acid solution of phenolsulphonphthalein was introduced. This was repeated one-half hour later, and the last meal was withdrawn at the end of the third half-hour period. There were thus used three distinct meals covering a period of one and one-half hours after the injection of histamine. The procedure was carried out at least four times on each dog on different days, and then the animal was subjected to the operative procedure. At the expiration of two weeks or longer four more experiments were done. Our results are thus based on observations on a minimum of four series of experiments, each consisting of three acid meals before operation and the same number after operation.

The chloride content of the acid meal was determined before it was introduced into the stomach. After each meal was removed from the stomach its quantity was measured and a sample was tested for bile by the Pettenkofer method. The percentage of phenolsulphonphthalein was determined by means of a colorimeter, and a portion was then analyzed for total and mineral chloride content. We have given elsewhere<sup>8</sup> details of the methods used to determine the concentration of chlorides, and these will not be repeated here.

#### CALCULATIONS

*Phenolsulphonphthalein Readings.*—This indicates the percentage of the original acid meal which is present per hundred cubic centimeters in the fluid removed from the stomach. Reduction in the percentage of phenolsulphonphthalein means that fluid has been added to the acid meal while it was in the stomach. This diluting fluid comes from three sources: (1) acid secreted by the stomach; (2) mucus secreted by the stomach, and (3) fluid regurgitated from the duodenum into the stomach.

*Determination of Chloride Content.*—*Total Chlorides:* This content, when determined on the acid meal before its introduction into the stomach, is all acid chloride. After the meal has been in the stomach, however, the total chloride content represents not only the acid chloride of the original meal and the chloride resulting from neutralization of some of the test meal but also the chloride which has been added by secreted mucus and acid and regurgitated duodenal fluid.

*Mineral Chloride:* This content is determined on the samples removed from the stomach and represents neutral chloride. It is the chloride of neutralized acid, secreted mucus and duodenal content.

*Acid Chloride:* This is the difference between the concentration of total chloride and that of mineral chloride. It represents unneutralized acid from the test meal and acid secreted by the stomach and not neutralized.

8. Wilhelmj, C. M.; Neigus, I., and Hill, F. C.: *Am. J. Physiol.* 106:381, 1933.

**Total Chloride Corrected for Dilution:** The chloride content of the original acid meal multiplied by the reading for phenolsulphonphthalein on the meal after its removal from the stomach represents the chloride content which the meal would have at that dilution if the diluting fluid contained no chloride.

**Extra Chloride:** Since the diluting fluid, whether derived from the stomach or from the duodenum, does contain chloride, the actual content of total chloride of the meal after its removal from the stomach is always higher than the figure obtained by correcting the original meal for dilution. The difference between the two figures is the extra chloride. This is the chloride of the secreted mucus, the acid and the duodenal contents.

**Acid Chloride Plus or Minus Corrected Value:** The content of acid chloride of the meal after its removal from the stomach may be greater or less than the chloride content of the original meal corrected for dilution. If it is greater the difference is due to acid secreted by the stomach. If it is less the difference represents neutralization.

**Total Fluid Entering the Stomach.**—The reading for phenolsulphonphthalein subtracted from 100 gives the number of cubic centimeters of fluid which diluted each 100 cc. of the test meal.

**Acid Fluid Entering the Stomach.**—We<sup>5</sup> have shown that the concentration of chloride of the fundic secretions averages 578 mg. per hundred cubic centimeters and that this is practically all acid chloride. Consequently, if the extra acid chloride of the sample is divided by 5.78, the quotient will be the number of cubic centimeters of acid fluid which entered the stomach and diluted each 100 cc. of the test meal.

**Extra Fluid.**—The difference between the amount of total fluid and the amount of acid fluid we have called the extra fluid. This is mainly derived from the duodenum and consists of bile, pancreatic juice and succus entericus. A small portion represents mucus secreted by the pyloric region of the stomach.

The table indicates the results obtained in a series of experiments on one dog before and after gastrojejunostomy. Because of lack of space all the data on the other experiments have not been given in tables, but the results are shown graphically in charts.

Three types of operation were performed: gastroduodenostomy, pyloroplasty and gastrojejunostomy. The gastroduodenostomy was an anastomosis between the upper portion of the duodenum, beginning about 3 cm. below the pyloric sphincter, and the anterior surface of the stomach. The pyloroplasty was of the Heineke-Mikulicz type, and at the conclusion of the operation the pylorus would easily admit two fingers. The gastrojejunostomy was performed by cutting the ligament of Treitz and making an anterior anastomosis beginning near the former point of attachment of the ligament on the jejunum. In a few instances we closed the pylorus at a subsequent operation by severing the stomach from the duodenum at the pyloric sphincter and suturing both stumps.

Chart 1 represents the difference between the total and the mineral chloride content, in other words, the acid chloride. This is the actual acidity of the meals after they are removed from the stomach, and if it is desired to translate the figures on milligrams of chloride per hundred cubic centimeters into terms of tenth-normal hydrochloric acid or total acidity they may be divided by 3.55. It will be noted at once when an acid meal is given to a normal dog and histamine is injected intramuscularly that during the first hour there is little reduction in the strength of the acid. Acid of the meal is neutralized, but it is replaced by acid secreted by the stomach. In dog D the strength of the acid, instead of being decreased, actually increased, and never during the one and one-half hour

*Complete Data as Obtained on Day C Before and After Gastrojejunostomy*

Solution	Hours	Total Chloride, Mg.	Mineral Chloride, Mg.	Total Chloride Minus Mineral Chloride, Mg.	Before Gastrojejunostomy			Chloride of Acid, ± Corrected Value	Volume, Cc.	Bile	Total Fluid Entering Stomach, Cc. per 100 Cc.	Fluid of Acid	Extra Fluid
					Phenol-sulphon-phthalcin, per Cent.	Chloride Corrected for Dilution, Mg.	Extra Chloride, Mg.						
0.102 normal hydrochloric acid, 353 Mg. chloride	1½	369	30	339	89	314	55	+25	310	0	11	1	7
	1	369	30	339	90	318	51	+21	246	0	10	3	7
	1½	354	44	310	93	328	26	-18	282	0	7	0	7
	½	372	31	341	89	314	53	+27	306	0	11	5	6
	1	390	30	360	83	293	97	+67	318	0	17	12	5
	1½	372	26	346	92	325	47	+21	296	0	9	3	5
	½	367	48	319	85	300	67	+19	233	0	15	3	12
	1	375	39	336	86	304	71	+32	332	0	14	6	8
	1½	366	26	340	90	318	48	+22	246	0	10	4	6
	½	372	30	342	89	314	58	+28	310	0	11	5	6
	1	366	19	347	93	328	58	+19	311	0	7	3	4
	1½	366	24	342	94	332	52	+10	355	0	6	2	4
After Gastrojejunostomy													
0.101 normal hydrochloric acid, 352 Mg. chloride	½	361	92	269	76	268	93	+1	306	++	24	0.2	23.8
	1	366	84	282	79	278	88	+4	340	+++	21	0.7	20.3
	1½	354	80	274	83	292	62	-18	280	+	17	0	17
	½	378	73	300	76	268	105	+32	316	++	24	6	18
	1	375	44	331	85	299	76	+32	246	+	15	6	9
0.101 normal hydrochloric acid, 348 Mg. chloride	1½	364	84	280	81	285	79	-5	306	+++	19	0	19
	½	366	84	282	74	258	108	+24	330	+++	26	4	22
	1	360	95	265	72	250	110	+15	330	+++	28	3	25
	1½	348	91	257	79	275	73	-18	316	+++	21	0	21
	½	372	89	283	73	254	118	+29	368	+++	27	5	22
	1	376	67	309	77	268	108	+41	270	++	23	7	16
	1½	354	80	274	84	292	62	-18	280	++	16	0	16

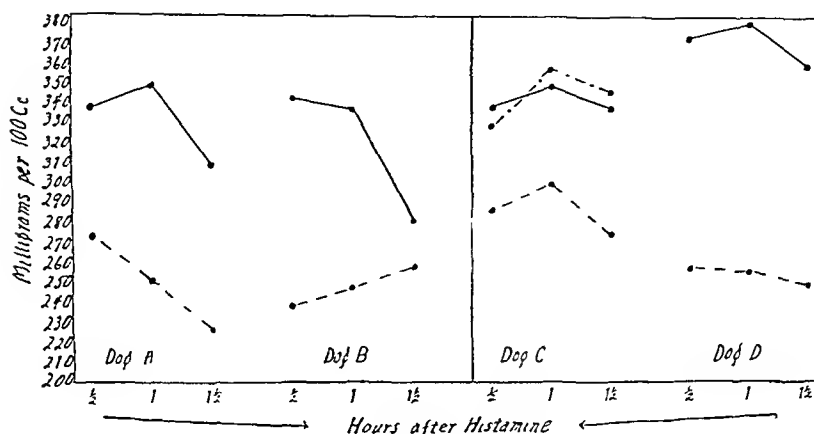


Chart 1.—The acid chloride content of the stomachs of dogs A, B, C and D at half-hour intervals after the administration of an acid meal containing 353 mg. of chloride per hundred cubic centimeters. The unbroken line represents the reading before operation; the broken lines for dogs A and B, the readings after gastroduodenostomy and for dogs C and D after gastrojejunostomy, and the line of dots and dashes, the readings after pyloroplasty.

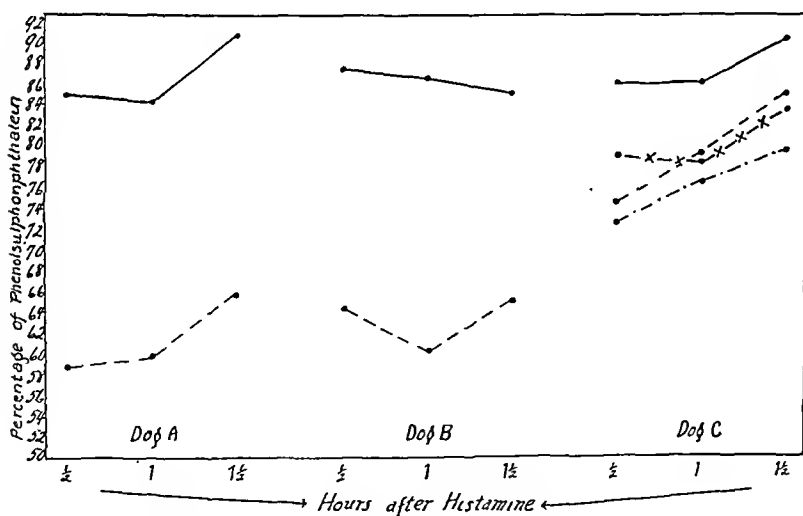


Chart 2.—The dilution of the meal in the stomach as shown by the reduction in the percentage of phenolsulphonphthalein. The unbroken line indicates the reading before operation; the broken line for dogs A and B, the readings after gastroduodenostomy; the line broken with crosses, the readings after pyloroplasty; the line of dots and dashes, the readings after gastrojejunostomy, and the broken line for dogs C and D, the reading after gastrojejunostomy plus closure of the pylorus.

period did it drop to the level of the original meal. In dogs A and B there was considerable decrease in the strength of the acid, but most of the decrease occurred during the third half-hour period, when the effect of the histamine had worn off and little acid was being secreted by the stomach.

After operation a striking change was seen. The acidity of the acid meal was reduced immediately and reached a much lower level. The only exception was seen in dog C, after a pyloroplasty which was done before the gastrojejunostomy. Another dog on which a pyloroplasty was performed but for which figures are not charted here showed the same findings as this one. The operation of pyloroplasty seemed to cause little or no change in the reduction of the acidity of an acid meal. We hesitate to draw conclusions from the results of these two operations, but the results were rather striking and would seem to warrant further investigation.

Chart 2 shows the percentage of phenolsulphonphthalein in the meals removed from the stomach, and obviously here is the explanation of most of the reduction in acidity noted in the previous chart. The curve of the reduction of acidity

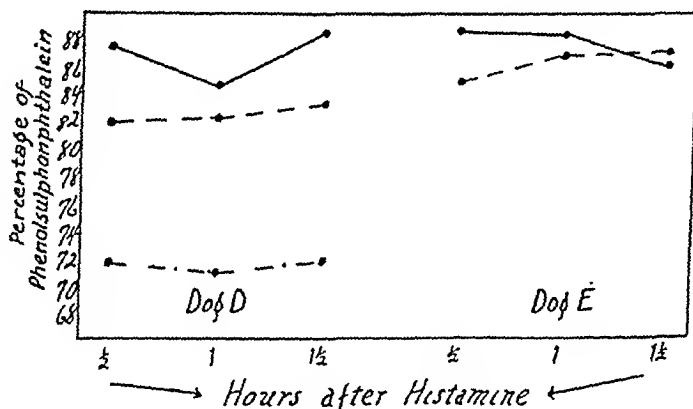


Chart 3.—The dilution of the meal in the stomach as shown by the reduction in the percentage of phenolsulphonphthalein. The unbroken line indicates the reading after operation; the line of dots and dashes, the readings after gastrojejunostomy; the broken line, for dog D, the readings after gastrojejunostomy plus closure of the pylorus, and the broken line for dog E, the reading after pyloroplasty.

corresponds closely with the curve for concentration of phenolsulphonphthalein; in other words, the reduction in the acidity of the acid meal is due mainly to dilution of the meal by nonacid fluid regurgitated into the stomach from the duodenum. In dog D it will be noted that there was a marked increase in the amount of dilution of the test meal after gastrojejunostomy was performed. When at a subsequent operation the pylorus was closed, the amount of dilution was considerably less. In dog C there was some increase in the amount of dilution of the test meal after pyloroplasty, but when gastrojejunostomy was performed later the dilution was increased. Closure of the pylorus again diminished the amount of dilution. Dogs A and B showed the marked increase in dilution which is produced by gastroduodenostomy. Dog E demonstrated the absence of notable change following pyloroplasty and showed why the strength of the acid remained unaltered, as shown in chart 1.

In charts 4, 5 and 6 we have represented graphically the nature and amount of the diluting fluid which enters the stomach. The total amount of fluid entering the stomach per hundred cubic centimeters of the test meal has been charted

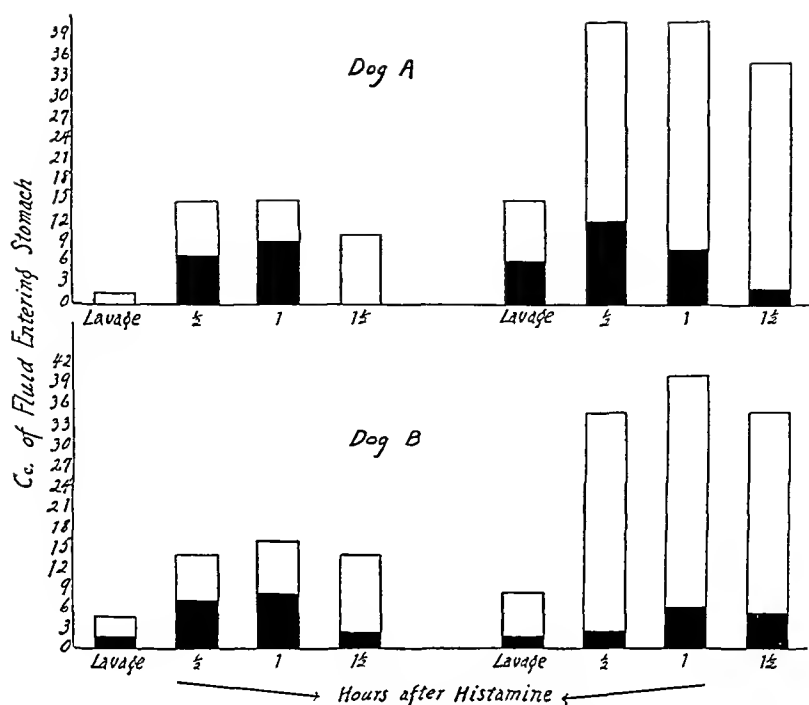


Chart 4.—The nature and the amount of fluid which diluted the test meal in dogs A and B before and after gastroduodenostomy. In this and the following charts the group of four columns on the left indicates the readings before the operation; the group to the right, the readings after the operation; the solid portion of the columns, the acid fluid, and the open portion, the extra fluid.

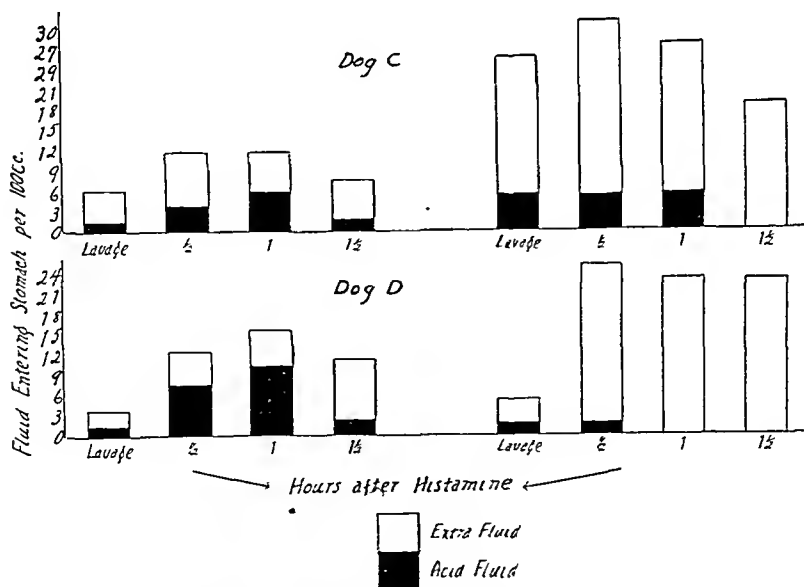


Chart 5.—The nature and the amount of fluid which diluted the test meal in dogs C and D before and after gastropylorostomy.



and divided, by the calculations already described, into acid fluid, that is, acid secreted by the stomach, and extra fluid or fluid entering the stomach from the duodenum and gastric mucus. It will be noted that there is practically no change after pyloroplasty but that gastro-enterostomy produces a marked increase in the total fluid entering the stomach per hundred cubic centimeters of the acid meal. The total volume of fluid actually removed from the stomach, but not charted here, was essentially the same before and after operation, varying from 240 to 325 cc. More of the meal had left the stomach after gastro-enterostomy than before, but its place was taken by extra fluid, which diluted the remainder of the meal and kept the volume unchanged. The amount of acid fluid will be seen to be practically the same before and after operation, and this in spite of the great amount of extra fluid present; so obviously the neutralizing power of this extra fluid is low. We<sup>7</sup> have previously shown that the reduction in acidity of an acid meal placed in the intact stomach is due 65 per cent to dilution and only 35 per cent to neutralization, and evidently here also a similar relation exists.

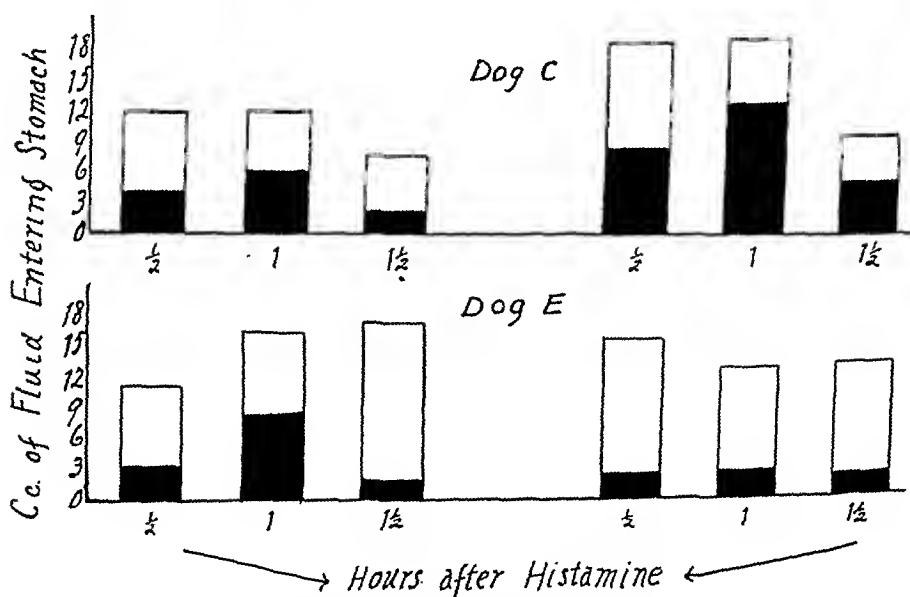


Chart 6.—The nature and the amount of fluid which diluted the test meal in dogs C and E before and after pyloroplasty.

In all experiments the amount of bile in the meals removed from the stomach was estimated by grading the strength of the Pettenkofer reaction from 1 plus to 4 plus, and in all cases the amount of bile present closely paralleled the amount of extra fluid. We have previously shown<sup>9</sup> in studies on pouches prepared from the pyloric region of the stomach that the amount of mucus the pylorus is capable of secreting is not great enough to be an important factor in the dilution of the test meal. The increased amount of bile present after gastro-enterostomy was confirmatory evidence that most of the extra fluid comes from the duodenum.

Another incidental finding to which we wish to call attention is the content of the stomach as found by lavage at the beginning of each experiment. Ordinarily the resting stomach of a normal dog contains little or no free acid, but after gastro-enterostomy has been performed considerable free acid is present. The

9. Wilhelmj, C. M., Neigus, I., and Hill, F. C.: *Am. J. Physiol.* **107**:490, 1934.

significance of this finding we are unable to explain, but it may have some etiologic relationship to the occasional occurrence of jejunal ulcer following gastro-enterostomy in dogs.

#### CONCLUSIONS

1. When an acid meal is introduced into the stomach of a normal dog and histamine is given intramuscularly, the strength of the acid shows little change or is increased during the first hour and then is gradually reduced. Reduction in the strength of the acid meal during the first hour is compensated for by acid secreted by the stomach. At the end of an hour the stimulus from the injection of histamine has worn off and the acid is usually reduced in strength. After gastro-jejunosomy the reduction in acidity is strikingly increased. After gastroduodenostomy the reduction is even more marked. After a Heineke-Mikulicz type of pyloroplasty the amount of reduction is almost the same as in a normal dog. After gastrojejunosomy plus closure of the pylorus the reduction is less marked than after gastro-jejunosomy alone.

2. The amount of dilution of the acid meal by duodenal fluid regurgitating into the stomach closely parallels the reduction in acidity and is the main cause of the reduction.

3. The total amount of fluid present in the stomach one-half hour after the introduction of an acid meal is the same after gastro-enterostomy as before, but this total fluid after operation contains a larger proportion of nonacid or "extra" fluid.

4. The amount of acid secreted by the stomach under stimulation with histamine and not neutralized is the same, per hundred cubic centimeters of the acid meal, after operation as before.

5. The amount of bile in the acid meals after removal from the stomach is directly proportional to the amount of extra fluid.

6. The resting stomach of a dog after gastro-enterostomy contains considerable free acid.

# FATAL CASES OF SEPTICEMIA CAUSED BY BACILLUS COLI FOLLOWING GASTRIC OPERATIONS

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A short time ago my interest was drawn to the possible fatal complication of septicemia caused by *Bacillus coli* following gastric operations. A woman 58 years old, in excellent condition before operation, died eighteen hours after a gastro-enterostomy with a temperature of 41.5 C. (106.6 F.) and signs of vascular collapse. *Bacillus coli*-communior was recovered in an antemortem blood culture. The postmortem examination revealed no evidence of localized infection, peritonitis or hemorrhage. Death was attributed to overwhelming *B. coli* septicemia.

The records of gastric operations at the University Hospitals for the last thirteen and one-half years,<sup>1</sup> exclusive of the cases of perforated ulcer, include another fatal case of bacteremia caused by *B. coli* proved by antemortem blood culture and a third case which was similar to these two in its clinical features but in which no blood culture was taken. Because no record of such cases has been found in a search of the literature it is felt worth while to report this possible complication following an operation on the stomach and jejunum.

CASE 1.—A 58 year old white housewife was admitted to the hospital for the third time on May 25, 1934. The history of the illness dated back twenty-one years and was that of gastric ulcer. A sleeve resection of the stomach had been performed in 1925 with resultant relief of symptoms for five years. In 1931 the symptoms reappeared, and they became very severe two months before the last admission to the hospital. The remainder of the history was irrelevant.

The physical examination revealed nothing suggestive of ulcer. On the basis of the history and fluoroscopic examinations a diagnosis of gastric ulcer with retention was made. On May 28 a posterior gastro-enterostomy was performed. Before the operation the temperature was 37.2° C. (98.6 F.), the pulse rate, 80, the respiratory rate, 20, and the blood pressure, 135 systolic and 80 diastolic. The white blood cell count was 8,400. The free hydrochloric acid was 10 degrees and the combined acid, 90 degrees.

The operation was performed with the patient under gas-oxygen-ether anesthesia and lasted two hours and forty-five minutes. The patient's condition at the end of the operation was good; the blood pressure was 110 systolic and 60 diastolic, the pulse rate, 140, and the respiratory rate, 32. Three hours later the patient was cyanotic and the blood pressure started to fall. Five and a half hours after operation the blood pressure was 60 systolic and 48 diastolic. After the

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From the Department of Surgery of the University Hospitals.

1. This includes the records of the Lakeside Hospital and the Hanna House.

subcutaneous administration of ephedrine and an intravenous injection of 10 per cent solution of dextrose the blood pressure rose to 90 systolic and 40 diastolic. Three and a half hours after operation the temperature was 37.6 C. (99.9 F.). Seven and a half hours after operation the temperature was 40 C. (104 F.), the pulse rate, 146, and the respiratory rate, 46. The patient's condition was critical. Examination of the lungs revealed only a few moist râles at the base of the left

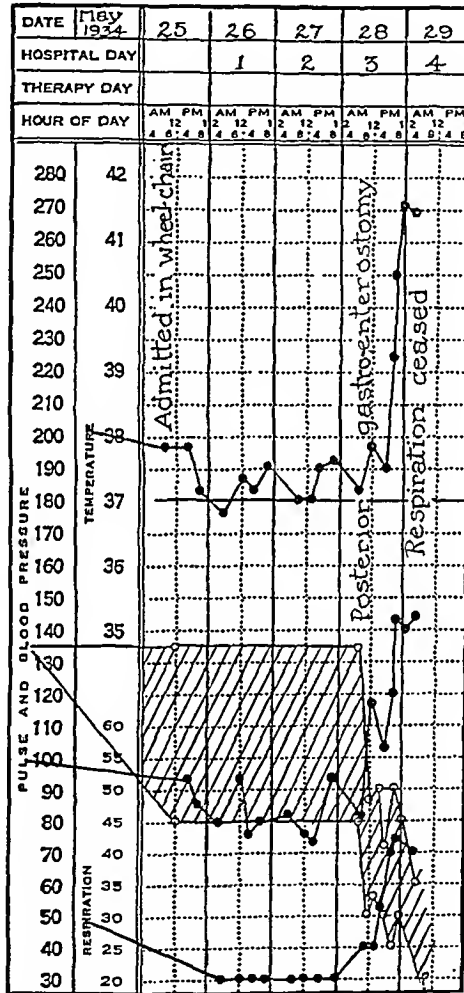


Chart 1 (case 1).—The record of temperature, pulse and respiratory rates and blood pressure immediately before and following the operation.

lung with no evidence of consolidation. The trachea was in the midline and the heart was normal, although the sounds were distant. The patient was not pale. Pneumonia, hemorrhage or septicemia was suspected. A stomach tube was passed and only a few cubic centimeters of blood-tinged fluid was obtained. The abdomen was soft and the stomach was not dilated. In spite of transfusion

of 500 cc. of whole blood and frequent administrations of caffeine sodiobenzoate the patient rapidly grew weaker. Eleven and a half hours after operation the temperature reached 41.6 C. (106.8 F.), the pulse rate was 140, the respiratory rate was 40, and the blood pressure was 80 systolic and 50 diastolic. The blood pressure continued to fall. Fourteen and a half hours after operation the temperature was 41.5 C., the pulse rate, 144, the respiratory rate, 30, and the blood pressure, 60 systolic and 32 diastolic. The pulse became weaker and the rate more rapid, and the patient died seventeen and a half hours after the operation. A blood culture made ante mortem was later reported to contain *B. coli-communis*. Though septicemia was suspected, the postoperative course was so short that only one blood culture was taken. Chart 1 shows the rapidly fatal course with the sharp rise in temperature and the fall in blood pressure.

Necropsy disclosed a small gastric ulcer, the recent gastro-enterostomy which was structurally sound, a moderate amount of bronchopneumonia and pulmonary edema, acute fibrinous pleuritis and an old surgical cicatrix of the stomach where the sleeve resection had been done. In addition, there were fatty infiltration of the liver and kidneys and some old peritoneal adhesions. A blood culture five and one-half hours after death showed *Bacillus alkaligenes*. *B. coli* was not recovered after death. Midway in the stomach there was a band of scar tissue which extended over both the anterior and the posterior surface from the lesser to the greater curvature, representing the site of the previous sleeve resection. On the posterior surface of the stomach at the pylorus there was a small ulcer measuring 6 mm. in diameter. This area was approximately 2 cm. from the band of scar tissue which extended across the midportion of the stomach. There was no evidence of localized infection, acute peritonitis or hemorrhage.

CASE 2.—A 56 year old white married laborer was admitted to the hospital on June 3, 1930, with a history of peptic ulcer. Since 1922 there had been periodic attacks of epigastric pain occurring two to three hours after eating and relieved by food. Roentgen examination on three occasions revealed a deformity of the duodenal cap. In 1924 the free hydrochloric acid after fasting was 74 degrees and the total acidity was 112 degrees. During the six months preceding admission to the hospital the patient had lost 20 pounds (9.1 Kg.) and for two months had vomited nearly everything he ate. The history was otherwise irrelevant.

The physical examination revealed a fairly well developed but poorly nourished man not acutely ill. Examination of the abdomen revealed tenderness on deep palpation in the epigastrium and on each side of the midline. The rest of the examination yielded negative results.

On the basis of the history and roentgen findings a diagnosis of duodenal ulcer with gastric retention was made. Before the operation the temperature was 36.8 C. (98.2 F.), the pulse rate, 80, the respiratory rate, 20, and the blood pressure, 130 systolic and 80 diastolic; gastric analysis showed free hydrochloric acid, 25 degrees, and combined acid, 16 degrees. The white blood cell count was 6,100; the hemoglobin content was 101 per cent, and the differential blood smear contained 77 per cent of polymorphonuclear leukocytes. The vomitus showed a coffee-ground appearance; the benzidine test for occult blood was positive.

At operation, with the patient under gas-oxygen-ether anesthesia, a duodenal ulcer and pyloric obstruction were found. The pylorus was resected, the end of the stomach and duodenum were closed and a posterior gastro-enterostomy (Billroth II) was performed. The operation lasted two hours and fifty minutes. The patient's condition immediately after operation was satisfactory. The blood pressure at the beginning of the operation was 110 systolic and 80 diastolic, rose to a maximum of 150 systolic and 110 diastolic and at death was 95 systolic and 70

diastolic. The pulse rate was 135 at the beginning of the operation, with a maximum rate of 175, and 145 at death. The respiratory rate averaged 30. Three hours postoperatively the blood pressure was 78 systolic and 60 diastolic, the pulse rate, 120, and of fair quality, and the respiratory rate, 28. The patient had short attacks of hiccup, and his hands appeared cyanotic. Examination of the chest

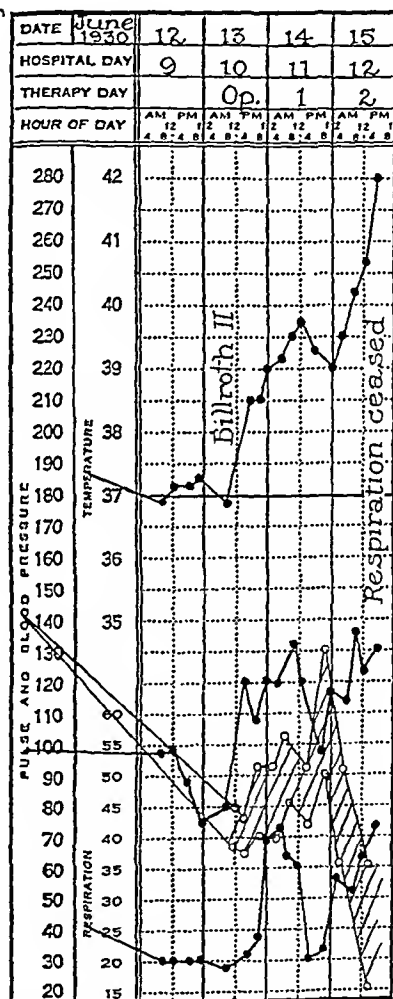


Chart 2 (case 2).—The record of temperature, pulse and respiratory rates and blood pressure immediately before and following the operation.

gave negative results. An infusion of physiologic solution of sodium chloride was given immediately after the operation. Because the blood pressure continued to be low, 300 cc. of a 10 per cent solution of dextrose was given intravenously eight hours after the operation. At this time the temperature was 38.5 C. (99.3 F.) and the blood pressure was 105 systolic and 85 diastolic. Twelve hours after the operation the temperature was 39 C. (102.2 F.), and the pulse rate,

120; the respiratory rate was 40 and there was a Cheyne-Stokes rhythm. The patient was placed on the "danger list." The following day the temperature remained elevated around 39.5 C. (103.1 F.); the blood pressure was 110 systolic and 80 diastolic, the pulse rate was 116, and the respiratory rate was from 22 to 36. The patient continued to have short attacks of hiccup. He was drowsy and slightly cyanotic.

Forty-eight hours after the operation the temperature was 41 C. (104.8 F.), the pulse rate, 124, the respiratory rate, 36, and the systolic blood pressure, 96. Examination of the heart and lungs again yielded negative results. The abdomen was everywhere soft. The patient did not appear anemic. The red blood cell count was 4,200,000; the hemoglobin content was 70, and the white blood cell count was 4,000. This low white blood cell count suggested the possibility of an overwhelming infection. Since there was no evidence of hemorrhage, a transfusion of blood was not given. The course was so rapid that it seemed to exclude the possibility of peritonitis. Septicemia seemed most likely. Accordingly, a blood culture was taken which was later reported to contain *B. coli*, the type not determined. In spite of the intravenous and subcutaneous administration of fluids, caffeine sodiobenzoate and digifolin, the patient rapidly became worse. The temperature rose to 42 C. (107.6 F.), the pulse rate was 130, the respiratory rate was 42 and the blood pressure was 60 systolic and 20 diastolic. The patient died fifty-two hours after the operation. Chart 2 shows the course of this patient.

Postmortem examination disclosed a recent gastro-enterostomy in which no structural defect could be demonstrated. There was a moderate amount of bronchopneumonia and pulmonary edema. About 250 cc. of old blood and blood clot were found in the peritoneal cavity but not enough to account for the collapse of the patient. There was no evidence of peritonitis or localized infection. A blood culture four hours post mortem revealed *B. coli-communior*.

CASE 3.—A 57 year old toolmaker was admitted to the hospital on Aug. 29, 1929, with symptoms suggesting carcinoma of the stomach. He complained of weakness, of tiring easily, of anorexia and of the loss of 12 pounds (5.4 Kg.) during the preceding two months. For a year he had noticed shortness of breath on exertion and tarry stools on several occasions. The remainder of the history was irrelevant.

He was well developed and well nourished with marked pallor of the skin and mucous membranes. There were no abdominal masses or tenderness. The rest of the examination revealed nothing remarkable.

The white blood cell count was 7,000; the red blood cell count, 3,000,000, and the hemoglobin content, 50. The blood smear presented achromia typical of secondary anemia, and a differential count showed 75 per cent polymorphonuclear leukocytes. The stool gave a strongly positive reaction to benzidine for occult blood. On the basis of the history and the roentgen finding of a large filling defect, a diagnosis of carcinoma of the stomach was made. Before the operation the temperature was 37.5 C. (97.3 F.), the pulse rate, 90, the respiratory rate, 20, and the blood pressure, 110 systolic and 68 diastolic.

On the eighth day of hospitalization, after a transfusion of 600 cc. of whole blood, a moderate-sized carcinoma of the pylorus was resected. The divided end of the duodenum was closed, and a loop of jejunum was anastomosed to the severed end of the stomach. The operation lasted about two and a half hours. During the latter part of the operation the blood pressure fell to 70 systolic and 35 diastolic but responded when dextrose was given intravenously. After the patient was returned to his room the blood pressure continued to be low. Seven hours after the operation the temperature was 38.6 C. (101.6 F.), the pulse rate,

132, the respiratory rate, 37, and the blood pressure, 80 systolic and 50 diastolic. Eleven and a half hours after the operation the temperature reached 40.3 C. (104.5 F.), the pulse rate was 144, and the respiratory rate, 32. A second transfusion of blood given fourteen hours postoperatively failed to improve the condition of the patient. The temperature remained around 40.5 C. (104.9 F.). The pulse became weaker and more rapid. Twenty-four hours after the operation the

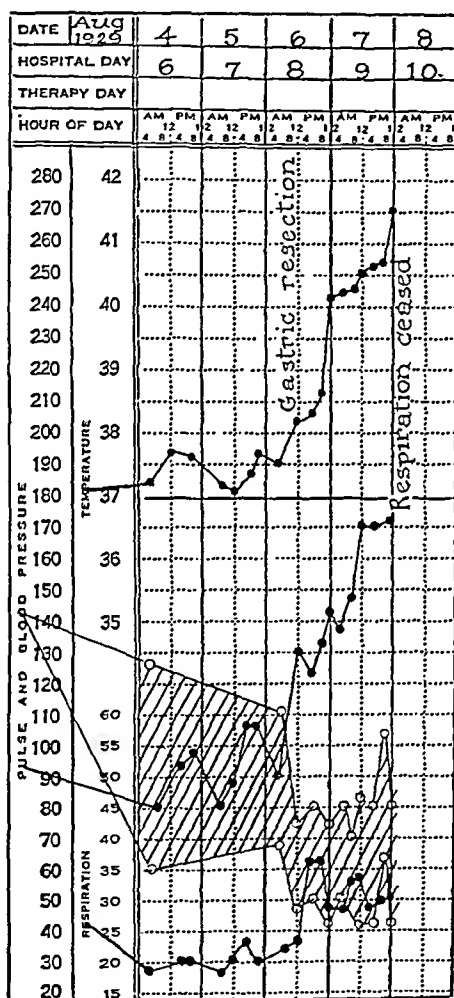


Chart 3 (case 3).—The record of temperature, pulse and respiratory rates and blood pressure immediately before and following the operation.

temperature was 40.5 C., the pulse rate, 172, the respiratory rate, 36, and the blood pressure, 84 systolic and 42 diastolic. Examination of the lungs and heart gave negative results. There was no evidence of peritonitis. Thirty-six hours after the operation the temperature rose to 41.5 C., the pulse became imperceptible, the respiratory rate was 36 and the blood pressure was 80 systolic and 45 diastolic.



The patient died forty hours after the operation. Postmortem examination was not permitted. Unfortunately, no blood culture was taken ante mortem. Chart 3 gives a graphic view of the clinical course of this patient, which is similar to that of the first two patients.

#### CASES REPORTED IN THE LITERATURE

It seems worth reporting these cases as in the early stage they simulate cases of hemorrhage, they seem to carry a fatal prognosis and no previous report has been found in a search of the literature. Wiens<sup>2</sup> in 1909 reported six cases of *B. coli* bacteremia, among which was one of a man 45 years old who had a gastrostomy for carcinoma of the esophagus. He died eight weeks after the operation. The ante-mortem blood culture contained *B. coli*. The cases described in this report, however, present a different clinical picture from that of Wiens' case except for the bacteremia. The literature to 1924 on *B. coli* bacteremia has been well summarized by Felty and Keefer<sup>3</sup> who reported twenty-eight cases of their own. In two of these cases the infection came from the intestinal tract. However, in none of their cases did injection follow an operation on the stomach. They stated that the reported cases of *B. coli* septicemia in which the intestine was regarded as the portal of entry complicated either acute inflammatory processes, like typhoid fever or dysentery, or were subsequent to appendiceal abscesses with thrombophlebitis or peritonitis. Neither in their report nor in those of others<sup>4</sup> is there any mention of cases like those just reported. The false impression might be gained from this that *B. coli* bacteremia is a rare complication of gastric surgical procedures.

#### COMMENT

In order to determine the frequency of complication the records of the University Hospital of cases of gastric operation exclusive of cases of perforated peptic ulcer were reviewed.<sup>1</sup> The cases of perforated ulcer

2. Wiens: *Zur Kasuistik der Kolibakteriämie*, München. med. Wchnschr. **56**:692, 1909.

3. Felty, A. R., and Keefer, C. S.: *B. Coli Sepsis*, J. A. M. A. **82**:1430 (May 3) 1924.

4. (a) Jacob, L.: *Ueber Allgemeininfektion durch Bacterium Coli commune*, Deutsches Arch. f. klin. Med. **97**:303, 1909. (b) Maher, S. J.: *Purpura Haemorrhagica: Is It Caused by the Colon Bacillus?* M. Rec. **75**:482, 1909. (c) Draper, G., quoted by Felty and Keefer.<sup>3</sup> (d) Tidy, H. L., and Pantón, P. N.: *A Note on the Occurrence of the Colon Bacillus in the Blood*, Lancet **2**:1500, 1912. (e) Holzman, A.: *Two Cases of Colon Bacteraemia*, Long Island M. J. **7**:376, 1913. (f) Widal, F.; Lemierre, A., and Brodin, P.: *Four Cases of B. Coli Septicemia*, Bull. et mém. Soc. méd. d. hôp. de Paris **44**:963, 1920. (g) Pope, B. A.: Quoted by Felty and Keefer.<sup>3</sup> Wiens.<sup>2</sup>

were excluded because it is known that *B. coli* may enter the blood stream in peritonitis. Therefore, it did not seem wise to include those cases in which peritonitis was present before operation. During the last thirteen and one-half years (from Jan. 1, 1921, to July 1, 1934), exclusive of the cases of perforated ulcer, there have been recorded four hundred and sixteen cases from both the private and the ward services at the Lakeside Hospital in which gastric operations have been performed. Of this number seventy-nine patients died in the hospital following the operation. Among these seventy-nine were the two cases reported here in which an antemortem blood culture was reported to contain *B. coli*. The third case described here closely resembled the first two cases clinically, but no antemortem blood culture or postmortem examination was obtained. In making the diagnosis of *B. coli* bacteremia it is recognized that the organism should be obtained from the blood during life.<sup>5</sup> It is significant to point out that the two cases of *B. coli* bacteremia in which the diagnosis was made by antemortem blood culture were of the same frequency as hemorrhage in this series of seventy-nine cases in which death followed operation. They constituted 2.6 per cent if all the cases of gastric operation were included: 3.3 per cent after gastro-enterostomy or partial gastrectomy or 4.5 per cent if the third case is included. My cases followed gastro-enterostomy or partial gastrectomy. Holzman<sup>46</sup> in 1913 aptly said that *B. coli* septicemia must always be borne in mind after an operation, especially after laparotomy. The table shows the causes of death following gastric operations and the frequency of *B. coli* septicemia. In cases 1 and 2 it is difficult to estimate the part played by the bronchopneumonia in the fatal outcome. All that can be said is that anatomically the bronchopneumonia was slight and that death occurred in a much shorter time than is usual in cases of bronchopneumonia. There was no evidence of collapse of the lungs in either case clinically or on the postmortem examination.

It is interesting to speculate on the train of events in these cases. That the operation started the lethal course is evident. It seems likely that the organisms were in the stomach at the time of operation and were thus introduced into the blood stream. It is well known that the stomach may contain *B. coli*. Cushing and Livingood<sup>6</sup> pointed

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5. Miller, J. L.: *Bacillus Coli Infections*, in Christian, H. A., and MacKenzie, J.: *Oxford Medicine*, New York, Oxford University Press, 1927, vol. 4, p. 763.

6. Cushing, H., and Livingood, L. E.: *Experimental and Surgical Notes upon the Bacteriology of the Upper Portion of the Alimentary Canal, with Observations on the Establishment There of an Amicrobic State as a Preliminary to Operative Procedures on the Stomach and Small Intestines*, Johns Hopkins Hosp. Rep. 9:543, 1901.

this out in 1901. Kopeloff<sup>7</sup> made bacteriologic studies on the gastric juice of 14 psychotic and normal patients by the Rehfuß method and found *B. coli* present in the patient with the highest gastric acidity. Gillespie<sup>8</sup> in 1892 reported the finding of *B. coli-communis* in the gastric contents of a patient suffering from gastric dilatation. Both Timozzi<sup>9</sup> and Lucksch<sup>10</sup> reported the finding of *B. coli* in the stomach of patients with pernicious anemia. These reports indicate that *B. coli* may be grown from gastric juice with a normal, low or high content of hydrochloric acid. Poppens<sup>11</sup> studied the bacteria of the fasting stomach and duodenum in dogs and found *B. coli* present in the gastric contents of four of fifteen animals and in the duodenum of twelve of fifteen animals after a period of fasting of from fourteen to twenty-two hours.

*Causes of Death Following Gastric Operations Exclusive of Operation for Perforated Ulcer*

	Cases		Cases Proved at Autopsy	
	Number	Percentage	Number	Percentage
Bronchopneumonia.....	27	34.0	15	55
Inanition.....	11	14.0	5	45
Peritonitis.....	10	12.8	7	70
Intestinal obstruction.....	6	7.0	3	50
Unknown.....	6	7.0	0	0
Pulmonary embolus.....	3	3.9	0	0
Heart failure.....	3	3.9	1	33
Hemorrhage.....	2	2.6	2	100
Septicemia caused by <i>B. coli</i> .....	2	2.6	2	100
Abscess of the lung.....	2	2.6	2	100
Suspected septicemia caused by <i>B. coli</i> .....	1	1.3	0	0
Mediastinitis.....	1	1.3	0	0
Uremia.....	1	1.3	0	0
Cerebral embolus.....	1	1.3	0	0
Thyroid crisis.....	1	1.3	0	0
Acute pancreatitis.....	1	1.3	1	100
Disrupted wound.....	1	1.3	0	0
Total.....	79		38	48

On the contrary, Palier,<sup>12</sup> in studying the bacteria in the gastric contents of thirteen human patients, failed to find *B. coli*. Three of these patients had carcinoma of the stomach, one pernicious anemia, four, hypochlorhydria, and five, hyperchlorhydria. Löhr<sup>13</sup> in 1926 studied the

7. Kopeloff, N.: Bacteriologic Studies of Gastric Fractions Obtained by the Rehfuß Method, *J. Infect. Dis.* **30**:613, 1922.

8. Gillespie, A. L.: The Bacteria of the Stomach, *J. Path. & Bact.* **1**:279, 1892.

9. Timozzi, F. P.: Colon Bacilli in the Digestive Tract, *Klin. Wchnschr.* **4**:1017, 1925.

10. Lucksch, F.: The Colon Bacillus in Pernicious Anemia, *Med. Klin.* **21**:1200, 1925.

11. Poppens, P. H.: The Bacteriology of the Fasting Stomach and Duodenum, *Am. J. M. Sc.* **161**:203, 1921.

12. Palier, E.: The Bacteria of the Stomach, *M. Rec.* **66**:801, 1904.

13. Löhr, W.: Bacteriology of the Stomach, *Zentralbl. f. Chir.* **53**:1618, 1926.

bacteria in twenty-two cases of perforated gastric or duodenal ulcer and concluded that in surgery of the stomach the colon bacillus was not greatly to be feared. Recent experiments by Johnson and Arnold,<sup>14</sup> who established gastric fistulas in dogs, indicate that the gastric acidity probably has a bacteriostatic power rather than a bactericidal action. These investigators injected *B. coli* into the previously established fistulas and found that when free acid was detected no viable bacteria could be demonstrated. However, if sterile solution of alkaline phosphate was introduced to neutralize the free acid the original test bacteria reappeared in the culture.

These cases are presented to draw attention to the possibility of *B. coli* septicemia following a gastric operation even though there is no postmortem evidence of localized infection, such as peritonitis, and that this condition may be rapidly fatal and simulate hemorrhage in the vascular collapse.

#### SUMMARY

This report is made in order to draw attention to the possible complication of septicemia following operations on the stomach and jejunum.

Two fatal cases, associated with *B. coli* in the blood stream as shown by antemortem blood culture, are reported. Death of one patient followed gastro-enterostomy for gastric ulcer and that of the other after partial gastric resection (Billroth II) for duodenal ulcer. A third case with similar clinical but without bacteriologic evidence is also discussed.

In the first and third cases no blood studies were made after operation. In the second case the white blood cell count showed leukopenia of 4,000. This aided in the differential diagnosis between overwhelming infection and hemorrhage.

The causes of death in 79 of a series of 416 patients on whom gastric operations were performed are listed. These operations did not include cases of perforated gastric ulcer.

In this series the same number of deaths was attributed to *B. coli* septicemia as to hemorrhage.

Cases of *B. coli* septicemia following operations on the stomach and jejunum may have a fatal prognosis and simulate hemorrhage in the sudden vascular collapse and rapidly fatal outcome.

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14. Johnson, T. M., and Arnold, L.: Has the Free Gastric Acidity Bactericidal or Bacteriostatic Power? *Proc. Soc. Exper. Biol. & Med.* 29:501, 1932.

# EXPERIMENTAL STAPHYLOCOCCIC SUPPURATIVE ARTHRITIS AND ITS TREATMENT WITH BACTERIOPHAGE

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Since d'Herelle's<sup>1</sup> discovery in 1917 of the phenomenon to which he applied the term bacteriophagy an extensive literature on the subject has accumulated, an increasing part of which has been devoted to the therapeutic use of this biologic principle in clinical medicine. Perhaps because of the dramatic nature of the phenomenon in the test tube, perhaps because the imagination is so fired by a principle which was to rid the world of bacterial diseases, there has often been a great deal of overenthusiasm in the claims advanced for the therapeutic effects of bacteriophage. Such overenthusiasm, born for the most part of insufficient observation or loosely controlled experiments, has given rise among many serious clinicians to a skepticism which denies to bacteriophage any place in the realm of therapeutics. The misfortune of this situation is that a valuable biologic principle is denied a trial by the very men whose work with it would be most reliable and most helpful. Clearly there is great need of accurate clinical observation on the use of bacteriophage and of carefully controlled experimentation with human beings and animals.

The series of investigations here reported was planned to determine the action of bacteriophage in vivo under conditions which are believed to be as near as possible to ideal for bacteriophagy in the animal body. Before the complicated problem of the action or failure of action of

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1. d'Herelle, F.: Immunity in Natural Infectious Diseases, Baltimore, Williams and Wilkins Company, 1924; The Bacteriophage and Its Behavior, Baltimore, Williams & Wilkins Company, 1926. d'Herelle, F., and Rakieten, M. L.: Susceptibility of Hemolytic Staphylococci to Bacteriophage, J. A. M. A. **100**:1014 (April) 1933.

bacteriophage in clinical cases can be attacked there should be an appreciation of what this substance can be depended on to do under controlled optimum *in vivo* conditions. The plan of the investigation was to produce in an animal having tissue reactions similar to those of man a surgical infection with a bacterium against which there exists a specific bacteriophage of known and reliable virulence; to treat this infection with the lytic agent at varying intervals after its production, and to control each lesion thus treated with a similar, untreated infection.

Adolescent male dogs of the hound type, weighing from 18 to 20 pounds (8 to 9 Kg.), were used throughout the experiments. A hemolytic strain of *Staphylococcus aureus* was used as the infecting agent, and in order to simulate a well known and serious lesion in a human being as closely as possible, a suppurative arthritis of the knee joint was produced in the animals. Attempts were then made to protect the joints against the infection by the use of bacteriophage. Two purposes were thus served by the experiments: The effect of the bacteriophage was tested under controlled conditions, and at the same time there was tried a new and possibly useful adjunct in the therapy of suppurative arthritis, a disease for which the treatment has long been notoriously unsatisfactory.

#### REVIEW OF THE LITERATURE

A survey of the literature shows that no such work has previously been done. That a closed cavity of the body can be protected against infection by bacteriophage was shown by Zaytseff-Jern, Harvey and Meleney,<sup>2</sup> who were able to protect mice against peritonitis due to *Bacillus coli* by local treatments with bacteriophage up to three and one-half hours after the production of the lesion. Walker<sup>3</sup> has studied the effect of bacteriophage in experimentally produced cutaneous infections. No work has appeared, however, on this type of treatment in cases of artificial staphylococcic infections in the joints.

The susceptibility of the staphylococcus to the lytic action of bacteriophages was discovered soon after the phenomenon was described for the dysentery bacillus, and many potent races of phage have been developed which cause rapid and complete lysis of this organism in the test tube. Clinical applications of this fact have, however, in the main, met with disappointment. The type of lesion which has given the most

2. Zaytseff-Jern, H.; Harvey, H. D., and Meleney, F. L.: *B. Coli Bacteriophage in the Treatment of B. Coli Peritonitis in Mice*, *Proc. Soc. Exper. Biol. & Med.* **29**:741, 1932.

3. Walker, J. E.: *Effect of Bacteriophage in Experimental Skin Infections*, *South. M. J.* **24**:1087, 1931.

satisfactory results with bacteriophage therapy has been that of staphylococcic infections of the skin, Raiga,<sup>4</sup> Petit de la Villéon,<sup>5</sup> Zaytseff-Jern and others having obtained consistently good and often spectacular results in the treatment of furunculosis and carbuncles. MacNeal has reported a suggestive series of cases of staphylococcic septicemia in which the patients were treated by bacteriophage, and in which the mortality was very low for this disease. In the control of infections of surgical wounds bacteriophage has proved to be a disappointment. Several surgeons have tried this method of treatment in cases of osteomyelitis, one of the most dreaded of staphylococcic infections, but none has substantiated or even approached the glowing results reported by Albee,<sup>6</sup> who claimed to have been invariably successful with bacteriophage in the treatment of one hundred patients with osteomyelitis.

In 1931 there appeared in the French literature a remarkable series of reports<sup>7</sup> in which patients with suppurative arthritis were said to have been cured by injections of bacteriophage into the joint without other surgical or bacteriologic treatment. The enthusiasm of the authors reached a climax when Mirallié and Thiéry<sup>8</sup> claimed that staphylococcus bacteriophage had cured patients with streptococcic and gonorrheal arthritis, respectively. Grégoire<sup>9</sup> raised a voice against their case reports and reminded the authors that patients with arthritides due to these two organisms frequently get well without any treatment other than aspiration. No one else has deemed it necessary to controvert the claims of Mirallié and Thiéry.

Rice<sup>10</sup> reported success in the treatment with bacteriophage of many types of staphylococcic infections, including suppurative arthritis. We have used it, in one case of purulent arthritis of the knee as an adjunct to arthrotomy and drainage, without an encouraging result.

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4. Raiga, A.: Bacteriophage in Treatment of Furuncles and Carbuncles of the Face, *Bull. et mém. Soc. d. chirurgiens de Paris* **24**:571, 1932.

5. Petit de la Villéon: Staphylococcic Bacteriophage in Carbuncles and Furunculosis, *Bull. et mém. Soc. de méd. de Paris* **137**:68, 1933.

6. Albee, F. H.: The Treatment of Osteomyelitis by Bacteriophage, *J. Bone & Joint Surg.* **15**:58, 1933.

7. Wiart, P., and Mirallié, C.: Arthrite suppurée du genou guérie sans arthrotomie et avec un résultat fonctionnel excellent à la suite d'injections de bactériophage, *Bull. et mém. Soc. nat. de chir.* **57**:234, 1931.

8. Thiéry, P.: Sur le bactériophage, *Bull. et mém. Soc. nat. de chir.* **57**:655, 1931.

9. Grégoire, R.: A propos d'une arthrite suppurée du genou guérie sans arthrotomie à la suite d'injections de bactériophage, *Bull. et mém. Soc. nat. de chir.* **57**:477, 1931.

10. Rice, T. B.: Use of Bacteriophage Filtrates in Treatment of Suppurative Conditions, *Am. J. M. Sc.* **179**:345, 1930.

Larkum,<sup>11</sup> in 1932, gave the calmest and most rational evaluation of bacteriophage in clinical medicine that has yet appeared, and his conclusions are good up to the present. In one sentence he well summed up the danger to scientific medicine of unscientific writings: "So infinite are the possibilities which the discovery of this principle (bacteriophage) has made apparent that it would be nothing short of a calamity to have its continued investigation retarded or even halted through the unbridled enthusiasm of those who, without regard to the mechanism of its action, make use of this principle whenever an opportunity presents itself." This author drew attention to the fact, first brought out by d'Herelle,<sup>1</sup> that lysis is not the only means by which bacteriophage influences the relation between the host and the infecting bacterium; indeed, it may be of much less importance in that relation than the effect on phagocytosis, on the opsonins of the blood and on the virulence of the bacteria even when not lysed. Larkum stated that the proteins in the filtrate of bacteriophage resulting from the destruction of the bacteria probably are responsible for some of the beneficial results in the treatment, as they act as vaccines. Rice stated the belief that the success of local treatment of staphylococcic infections with bacteriophage is due to the combined action of the bacteriophage and antiviral. It is certain that, as Larkum said, "even without lysis, bacteriophage may considerably alter the course of an infection."

D'Herelle, Larkum, Applebaum and MacNeal,<sup>12</sup> Colvin,<sup>13</sup> Arnold and Weiss<sup>14</sup> and others have contributed much to the literature on the reasons for the failure of bacteriophage to produce lysis in the body of animals. The factors which are considered at present to be the chief inhibitors of this phenomenon *in vivo* are: (1) the inactivating influence of serum and exudates on bacteriophage, (2) the inhibition of bacteriophage by extracts of the bacteria and (3) the antigenic properties of bacteriophage, because of which inactivating antibodies are produced in the blood stream. Normal human blood serum is known to inhibit lysis *in vitro*. There is as yet no information on the influence of the fluid in the joints or of dogs' serum on lysis in the test tube.

There is considerable disagreement as to the importance of the serum antiphages in patients or animals treated with bacteriophage.

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11. Larkum, N. W.: Therapeutic Use of Bacteriophage, *J. Lab. & Clin. Med.* **17**:675, 1932.

12. Applebaum, M., and MacNeal, W. J.: Influence of Pus and Blood on the Action of Bacteriophage, *J. Infect. Dis.* **49**:225 (Sept.) 1931.

13. Colvin, M. G.: Behavior of Bacteriophage in Body Fluids and Exudates, *J. Infect. Dis.* **51**:527 (Nov.-Dec.) 1932; Relationship of Bacteriophage to Natural and Experimental Diseases of Laboratory Animals, *ibid.* **51**:17 (July-Aug.) 1932.

14. Arnold, L., and Weiss, E.: Antigenic Properties of Bacteriophage, *J. Infect. Dis.* **34**:317 (March) 1924.



Raiga, Gratia,<sup>15</sup> Sauv <sup>16</sup> and others, especially those of the French school of bacteriologists, have stated the belief that the antiphages are of great importance, and they have gone to complicated lengths, such as the employing of autohemotherapy, to overcome their action. Larkum, Zaytseff-Jern and other American authors have come to consider them of very little clinical significance.

The literature on the subject of the treatment of acute suppurative arthritis was reviewed by one of us<sup>17</sup> in a recent paper. It is a disease of great seriousness and often of dire consequences, and the proper method for its surgical treatment is still a matter of dispute. It would indeed be a boon to the surgeon if bacteriophage therapy could be depended on as an adjunct to the surgical drainage of these severely damaged joints.

No references were found in the literature on the production of experimental suppurative arthritis in dogs. It is common knowledge that most of the laboratory animals have a high resistance to staphylococcal infections. This is especially true of the guinea-pig. Other animals, however, notably the rabbit, are extremely susceptible to lesions of the joints; Key<sup>18</sup> has produced the changes of chronic arthritis in this animal by the injection of many substances, even such bland ones as salt solutions and distilled water. The dog, coming between these two extremes and reacting more nearly like man to the staphylococcus, is therefore a more suitable animal for these experiments.

#### EXPERIMENTAL PROCEDURES

The first problem was the production of a satisfactory purulent arthritis. To determine the course of an untreated staphylococcal infection of a joint in the dog, a series of six of these animals was used. Into the suprapatellar pouch of the left knee, with aseptic technic, was inoculated an eight hour culture of a hemolytic strain of *Staph. aureus* in a meat infusion-peptone broth medium of  $p_H$  7.8. It is realized that this procedure does not exactly simulate a hematogenous, embolic suppuration as it occurs in human synovial membrane, but the resemblance is probably as close as that attained by many experimental surgical procedures and the process is as close to the pathogenesis of the human lesion as can be secured.

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15. Gratia, A.: Le traitement des infections   staphylocoques par le bact riophage et les mycolysats staphylococciques, *Bull. et m m. Soc. nat. de chir.* **56**:345, 1930.

16. Sauv , L.: A propos due bact riophage, *Bull. et m m. Soc. nat. de chir.* **56**:348, 1930.

17. Inge, G. A. L., and Liebolt, F. L.: The Treatment of Acute Suppurative Arthritis; Report of Thirty-Six Cases Treated by Operation, *Surg., Gynec. & Obst.* **60**:86 (Jan.) 1935.

18. Key, J. A.: Production of Chronic Arthritis by Injection of Weak Acids, Alkalies, Distilled Water, and Salt Solutions into Joints, *J. Bone & Joint Surg.* **15**:67, 1933.

The anatomy of the dog's knee joint is peculiar in that the extensor digitorum longus muscle arises by a tendon from the lateral condyle of the femur, traverses the joint and passes out of it distally through a well defined sheath, thus forming a communication between the cavity of the joint and the muscle compartments of the leg. In a few of the dogs the infection spread into the leg by this route.

So that we might find the most efficient pathogen, various strains of staphylococcus were tried in the experiments, and the dosage of bacteria was varied. "Staphylococcus C," for example, was a stock hemolytic strain of *Staph. aureus* which had been on agar slants for months, used in the propagation of bacteriophage, and "Staphylococcus F" was a recently isolated strain from a virulent infection of a wound.

#### SERIES I

The series consisted of six dogs. The left knee was infected; the right was left normal as a control. The dogs were killed at varying intervals after operation for autopsy studies.

Dog 3.—Three hundred million bacteria (*Staph. C*) in 3 cc. of broth were injected into the left suprapatellar pouch without anesthesia. There was slight pain from distention when the last cubic centimeter was injected. The dog did not limp immediately. Four hours later he was acutely ill; the knee was swollen, warm and tender and held rigid. The dog was apathetic and had no appetite. After three days the animal began to improve; he would stand and eat but always held the left foot off the floor. Distemper developed on the sixth day, and the dog was chloroformed on the ninth day. Roentgenograms of the knee showed effusion but no thinning of the joint space and no destruction of the bone. Culture of the knee showed nonhemolytic *Staph. aureus*.

At autopsy the right knee was found to be normal. The left knee was moderately swollen; when the joint was opened, 2 cc. of thin gray pus escaped. The synovial membrane was greatly thickened, injected and grayish red; it averaged 4 mm. in thickness. There were large synovial villi in the suprapatellar pouch and over the pad of patellar fat. Pus did not extend into the leg. The bone, auricular cartilage and menisci were normal.

Microscopic sections of the right knee showed a normal synovial membrane. Section of the left knee showed that this membrane was greatly thickened, being from 15 to 20 cells in thickness and edematous, with moderate formation of villi and erosion of the surface layers of the cells. The subsynovial tissues were thickened and edematous, and the blood vessels had increased in number and were injected. The synovial membrane and the subsynovial tissues were markedly infiltrated with polymorphonuclear leukocytes.

Dog 4.—Six hundred million bacteria (*Staph. C.*) in 3 cc. of broth were injected. Within a few hours severe arthritis developed, with hot, tense swelling, pain, tenderness and pitting edema in the leg from the knee to the ankle. There was a marked general reaction, with a hot, dry nose, apathy and loss of weight. The animal began to improve on about the tenth day, and on the twenty-first day some weight was borne on the affected leg, and the swelling and tenderness disappeared. Mild distemper was present from the fourteenth to the nineteenth day; the animal recovered. Aspiration of the knee on the twelfth and on the seventy-first day gave pure cultures of nonhemolytic *Staph. aureus*. The knee at times remained symptom-free and apparently normal; at other times, especially in bad weather, it became swollen, warm and painful. The dog was in good general health, and the knee was inflamed when he was killed with chloroform on the

ninety-first day after operation. Roentgenograms at this time showed swelling of the soft tissue and a slight thinning of the joint space, but no destruction of the bone. Culture of the knee at autopsy showed hemolytic *Staph. aureus*.

At autopsy the left knee showed about the same picture as that seen in dog 3, except that the process was much more marked, and in addition there were three areas of erosion of the articular cartilage, the largest of these being 4 mm. in diameter with erosion of the bone at the depth. The cruciate ligaments were covered with hypertrophied synovial membrane, and the menisci were yellowish but otherwise normal.

Microscopic sections showed marked proliferation of the synovial membrane and its infiltration with polymorphonuclear leukocytes and fibroblasts. The vessels were numerous, and there was some perivascular round cell infiltration in places. The subsynovial areolar tissue was hypervascular, with moderate polymorphonuclear infiltration. The staphylococcus recovered from this knee (now called *Staph. D-4*) was used as the infecting organism for all the dogs of series IV and V.

Dog 27.—Three hundred million bacteria (*Staph. F*) in 2 cc. of broth were injected. This amount of broth caused no distention and no pain. Moderately severe arthritis developed which persisted until the dog's death from distemper on the eleventh day after operation. Culture yielded hemolytic *Staph. aureus*.

Autopsy showed a slight serosanguineous exudate and a slightly thickened synovial membrane which was quite injected. The articular cartilage was intact but showed several areas of purplish-red discoloration.

Microscopic sections showed moderate proliferation of the synovial membrane averaging from 12 to 15 cells in thickness, marked infiltration with leukocytes and extensive erosion of the surface layers.

Dog 28.—This dog received the same injection as dog 27. Clinically the condition was moderately severe arthritis without much general reaction, from which the dog completely recovered by the twenty-first day. The injection was repeated on the sixty-seventh day, causing mild transient arthritis which lasted seven days. On the ninetieth day after the original operation the animal was given an injection into each knee; mild acute arthritis developed, lasting six days on the left side and fifteen on the right side, with no general reaction. The animal was killed with chloroform on the one hundred and twenty-third day (thirty-three days after the last injections). Cultures of both knees showed nonhemolytic *Staph. aureus*.

At autopsy both joints appeared practically normal except for slight redness between the femoral condyles.

Microscopic sections showed very slight thickening of the left synovial membrane and an occasional leukocyte; the right knee was normal. This dog was obviously very highly resistant to the staphylococcus.

Dog 29.—Six hundred million bacteria (*Staph. F*) in 2 cc. of broth caused a moderately severe lesion with a slight general reaction, from which the dog recovered in five weeks. On the sixty-seventh day after operation an injection of one million bacteria (*Staph. 1968*) was given into the same knee. This caused only slight arthritis with little general reaction, from which the dog recovered in one week. He was killed on the one hundred and twenty-fourth day after the first, and fifty-seven days after the second, injection. Roentgenograms showed no pathologic condition. Culture of the left knee showed no growth after seventy-two hours.

Microscopic sections showed moderate thickening of the synovial membrane and a very light leukocytic infiltration; there were no polymorphonuclears in the subsynovial tissue. Grossly the joint showed little abnormality, there being slight synovial thickening and some superficial erosion of the articular cartilage on the femoral condyles.

Dog 30.—Six hundred million bacteria (Staph. F) in 2 cc. of broth were injected. Moderately severe acute arthritis occurred, which, however, cleared up spontaneously by the thirteenth day. There was no general reaction. The animal was killed with chloroform because of distemper on the sixteenth day. Roentgenograms showed no pathologic condition, and the culture showed no growth after seventy-two hours. Grossly and microscopically the joint appeared to be normal. This was a case of transient acute arthritis in a dog with a very high resistance.

*Summary.*—Of six dogs infected there were one with a severe, three with a moderate and two with a mild infection. One dog with a mild infection had received repeated injections of bacteria. The dose apparently played no part in the variation, since the severest and the mildest infection were caused by the same dose. Evidently there is a great variation among dogs of the same sex, size and age in their resistance to staphylococcic infections. Untreated staphylococcic purulent arthritis in the dog seemed to be no great threat against life and even in the severest case tended to subside spontaneously, leaving more or less structural damage but never any great disorganization of the joint or impairment of its function.

## SERIES II

Having determined that purulent arthritis could be produced, we next proposed to determine the effect of repeated injections of bacteriophage alone into normal joints and of broth alone into control joints. Such a norm had to be established before accurate interpretations could be made of the treated knees in the later series. For this purpose four dogs were used. The broth was the same as that used in the bacterial cultures; the phages were the filtrates from completely lysed cultures of *Staph. aureus* in broth, after they had been passed through Chamberland L3 filters and tested for potency *in vitro*. Two potent races of phage were used, one (BLS) having been obtained indirectly from Dr. A. Gratia of Brussels, the other (B59A) indirectly from Dr. N. W. Larkum of Michigan.

Dog 1.—Three cubic centimeters of BLS bacteriophage was injected into the left knee joint. Three cubic centimeters of broth was injected into the right knee joint. There was no early or late evidence of pain in the joints. On the seventh day both injections were repeated, but 2 cc. was used. No evidence of arthritis developed. The dog was killed with chloroform on the twentieth day because of distemper. Roentgenograms showed no pathologic condition. No bacteriophage was recovered from the left knee. Autopsy revealed two grossly normal joints. Sections were unsatisfactory, and the condition of the synovial membrane could not be judged.

Dog 2.—This dog was given the same injections as those first employed for dog 1. Except for slight distention with the injections there were no symptoms or signs of arthritis in either knee. The injections were repeated at about nine day intervals for ninety days, a total of ten injections being made into each knee.

There were no symptoms following the first six injections; the fluid was quickly absorbed. After the eighth injection after operation the dog limped on his left leg for a few hours. The dog's general health was unaffected until it was killed on the ninetieth day. Roentgenograms at this time showed no pathologic condition. Cultures showed no growth, and no bacteriophage was recovered from the left knee. At autopsy the right knee showed no excess fluid, but there was a slight injection of synovial membrane around the patellar pad of fat; the left knee contained a few drops of serous fluid, and the membrane was slightly thickened and injected throughout. Sections showed a normal synovial membrane on the right; on the left, there were slight proliferation of the synovial layer, increased formation of villi and patchy infiltration with leukocytes. The subsynovial tissues were normal.

Dog 287.—An injection of 8 cc. of B 59 A bacteriophage was made into the left knee, the joint being distinctly distended; light ether anesthesia was used. One hour later an attempt was made to aspirate some of this phage to test its potency after it had come into contact with the fluid of the joint and the tissues. All the fluid had been absorbed by that time, and none could be aspirated. The dog showed no evidence of arthritis. The injection was repeated four days later, the aspiration being done thirty minutes after injection; most of the fluid had been absorbed, so that only a few drops were recovered. This fluid, when tested against a fresh culture of staphylococci, showed no lytic action. The dog showed no evidence of arthritis; he died of distemper on the eleventh day; the body was destroyed by mistake, so that no autopsy was performed.

Dog 288.—An injection of 8 cc. of B 59 A bacteriophage was made into the left knee under light ether anesthesia. Thirty minutes later distention had disappeared; no fluid could be aspirated. The injection was repeated two days later; after fifteen minutes aspiration yielded 0.5 cc. of blood-tinged fluid which caused partial lysis of a culture of staphylococci in vitro and a few plaques when plated on agar. A third injection was given three days later, and aspiration after five minutes yielded about 1 cc. of fluid which caused three plus lysis in the test tube and showed numerous plaques on agar. The dog showed no evidence of arthritis at any time. Autopsy was not performed.

*Summary.*—Four dogs were used as a control series to determine the effect of bacteriophage alone and of plain broth alone on a normal joint. Of four joints into which injections of bacteriophage had been made, only one showed arthritis, and this was of mild degree following ten injections. The two knees into which sterile broth was repeatedly injected showed no evidence of arthritis clinically or at autopsy. When attempts were made to aspirate bacteriophage from the knee, it was found that the fluid was rapidly absorbed; when fluid was recovered, after being in the joint for thirty minutes, it had entirely lost its lytic action, and after being in contact with the interior of the joint for fifteen minutes it was only weakly active, in spite of the fact that it was of high virulence when injected.

### SERIES III

In this series of four dogs suppurative arthritis was produced in the knee by the technic used in series I and the lesion treated at various intervals by the injection of bacteriophage. Because of the wide variation in the susceptibility of

individual dogs to staphylococcic infection, as shown in series I, it was decided that each dog must furnish his own control for the treated joint; therefore, both knees of each animal were simultaneously given injections of equal numbers of staphylococci. One of the knees (the left) was then treated with bacteriophage, the other remaining untreated as a control. In this manner the error due to individual reactions was largely eliminated, but care had to be taken not to kill the dog with too great an infection.

Dog 79.—An injection of 300,000,000 bacteria (Staph. F) was made into each knee without anesthesia. Twenty-four hours later there was severe arthritis in both knees, with a moderate general reaction; the left knee received 2 cc. of bacteriophage. This treatment was repeated every two days, the dose ranging from 0.5 to 2 cc., depending on the amount of distention present in the joint; six treatments, a total of 8.5 cc., were given. The treated knee presented clinically and at autopsy acute purulent arthritis just as severe or perhaps a little worse than that shown by the control knee. Roentgenograms taken before autopsy was performed showed equal swelling of the soft tissue in the two knees, and the pathologic symptoms were grossly and microscopically about the same on the two sides. Cultures of the right knee showed nonhemolytic Staph. aureus; those of the left knee, the same organism, plus the presence of a weak bacteriophage. The dog was killed on the thirteenth day.

Dog 80.—Three hundred million bacteria (Staph. F) in 1.5 cc. of broth were injected into the right knee, and 300,000,000 bacteria (Staph. F) suspended in 1.5 cc. of B 59 A bacteriophage, into the left knee. In both joints there developed moderately severe arthritis, of the same degree on each side. The left knee then received twelve injections of bacteriophage at forty-eight hour intervals, the doses varying as for dog 79. Both lesions began to subside on about the fourteenth day, and there was no difference between the two joints either clinically or at autopsy. Sections showed the same degree of pathologic change in each knee. Cultures of both knees showed nonhemolytic Staph. aureus, and no bacteriophage was recovered from the left knee at autopsy. The dog was killed on the thirty-fifth day.

Dog 81.—This animal was given the same injections as dog 80. He was treated with thirteen injections of bacteriophage in the left knee over a period of twenty-three days. Clinically and by gross and microscopic examination at autopsy the treated left knee presented much more severe arthritis than did the right knee. Cultures of both knees at autopsy gave no growth.

Dog 82.—This dog was given the same injections as dog 79. The first operation consisted in the injection of bacteria only. Treatment of the left knee began after twenty-four hours. Thirteen injections of bacteriophage were given in twenty-three days. Clinically and at autopsy the treated left knee showed the more severe arthritis. Cultures of both knees showed no growth.

*Summary.*—In four dogs suppurative arthritis was produced in both knees. In two dogs the left knee was treated with bacteriophage simultaneously with the bacterial inoculation; in the others the first treatment with bacteriophage was given twenty-four hours after the bacterial inoculation. In all four dogs the treatment with bacteriophage was repeated every forty-eight hours until the animal was killed. In one dog there was not much difference between the two joints clinically or at autopsy, and in the other three dogs the treated knee was more severely damaged than the control knee.

## SERIES IV

Because of the aforementioned results, all attempts to treat the knees after the infection had become well established were given up, and it was decided that the first determination to be made was whether bacteriophage injected simultaneously with bacteria could protect a joint against infection. Since it was possible that the repeated injections of phage were the cause of more damage to the joint by trauma from the distention, it was also decided that in this series only one treatment with phage would be given and that simultaneously with the bacteria. In all the animals of this series the strain of staphylococcus used was Staph. D-4, a hemolytic organism which was recovered from the knee of dog 4, series I. The bacteriophage used was B 59 A.

Dog 116.—Three hundred million bacteria (Staph. D-4) in 1 cc. of broth were injected into the right knee, and 300,000,000 bacteria (Staph. D-4) in 1 cc. of B 59 A bacteriophage, in the left knee. Acute arthritis of moderate severity developed in both knees; it was slightly worse in the left knee clinically and subsided in both knees on about the eighth day. The animal was killed on the eleventh day. Autopsy showed changes of moderate acute synovitis equal in the two knees. Roentgenograms taken before autopsy was performed showed no abnormalities, and cultures of both knees remained sterile.

Dog 117.—This dog was given the same injections as dog 116. Severe arthritis developed in both joints, with a marked general reaction. Clinically and pathologically the left knee was less severely damaged than the right. The latter contained 3 cc. of pus from which nonhemolytic Staph. aureus was cultured; the left contained 1 cc. of serous fluid which was sterile but contained no demonstrable bacteriophage. Autopsy was performed on the eighth day.

Dog 118.—This dog was given the same injections as dog 116. Severe arthritis, clinically about the same on the two sides, was present. The dog died twenty-four hours after operation, probably of an embolus. At autopsy the treated knee was less severely damaged than the control. The right knee contained 3 cc. of thin gray pus which yielded hemolytic Staph. aureus; the left knee contained 3 cc. of serosanguineous exudate which was sterile and from which no bacteriophage was recovered.

Dog 119.—This dog was given the same injections as dog 116. Clinically and pathologically the treated joint was less damaged than the control joint. At autopsy on the eighteenth day the treated knee was almost normal; severe arthritis developed in the right knee. Culture of the right knee yielded hemolytic Staph. aureus and a hemolytic streptococcus (contamination?); culture of the left knee yielded no growth, and no phage was recovered.

Dog 88.—This dog was given the same injections as dog 116. Arthritis of moderate degree developed, lasting only twelve days in the right and eleven days in the left knee. Clinically and pathologically the treated knee was slightly worse than the control. Culture of both knees yielded nonhemolytic Staph. aureus. No bacteriophage was recovered from the left knee. The animal was killed on the twenty-second day.

Dog 108.—This animal was given the same injections as dog 116. There was severe arthritis in both knees, persisting up to death on the twenty-eighth day after operation. Neither clinically nor pathologically was there any difference between the two joints. Culture of both knees yielded hemolytic Staph. aureus; no bacteriophage was recovered from the left knee.

Dog 112.—This animal was given the same injections as dog 116. There was a moderately severe lesions, of equal degree in the two knees, subsiding on about the twentieth day after operation. In both knees the pus burrowed into the leg along the tendon of the extensor digitorum longus muscle. Autopsy on the thirty-second day showed that the two joints were about the same. Cultures of both knees remained sterile. This dog was a female, the only one used in the entire series.

Dog 122.—This animal was given the same injection as dog 116. There was a severe lesion in both knees, with a marked general reaction. Clinically and pathologically the treated knee appeared less damaged, though at autopsy severe synovitis was found in both joints. The organism was recovered from the right knee; culture of the left knee was sterile, with no demonstrable bacteriophage. The dog was killed on the fifteenth day.

Dog 123.—Three hundred million bacteria (Staph. D-4) in 1 cc. of broth were injected into the right knee, and 300,000,000 bacteria (Staph. D-4) in 1 cc. of B 59 A-4 bacteriophage (a specific phage, prepared with Staph. D-4 instead of with stock strains) were injected into the left knee. The right knee showed severe acute arthritis persisting until the animal was killed with chloroform on the eighteenth day. The left knee showed moderate arthritis, which had subsided by the eighth day. At autopsy there was a marked difference between the two joints in favor of the treated side. Culture of the right knee yielded hemolytic Staph. aureus; that of the left knee yielded no growth, and no phage was recovered.

Dog 124.—This animal was given the same injections as dog 123. A severe lesion with marked constitutional symptoms developed in both knees; it began to subside on about the thirteenth day after operation. Clinically and at autopsy the treated knee was more severely affected than the control. The dog was killed with chloroform on the twenty-first day. Culture of both knees yielded nonhemolytic Staph. aureus.

Dog 125.—This animal was given the same injections as dog 123. Moderately severe lesions developed which persisted until death from chloroform on the twentieth day, with a moderate general reaction. Clinically and at autopsy there was less damage to the treated knee than to the control. A slight amount of serous fluid was present in each knee, which on culture remained sterile.

Dog 126.—Injections were given as for dog 123. Severe acute suppurative arthritis persisted in the right knee with death on the twenty-first day, autopsy showing a badly inflamed joint with pus which yielded hemolytic Staph. aureus. A much less severe clinical infection developed in the left knee, which showed at autopsy only mild synovitis with some serous fluid from which the organism was recovered; the condition in the left knee subsided clinically by the thirteenth day.

Dog 133.—Injections were given as for dog 123. In the right knee a severe lesion developed which persisted until death on the fifth day; there was 3 cc. of pus in the joint, and marked synovitis was observed at necropsy. In the left knee distinct but less severe synovitis developed; there was no pus in the joint when it was opened. The dog walked on this leg on the fourth day. Culture of both knees revealed nonhemolytic Staph. aureus.

Dog 134.—Injections were given as for dog 123 except that in the right (control) knee some of the injected fluid penetrated into the subcutaneous tissues instead of into the joint. The dog became very ill, and a severe inflammatory reaction developed in both knees. Clinically and by gross and microscopic examination at autopsy the left (treated) knee was more severely damaged than the control. The organism was recovered from both joints. The animal was killed on the fifth day.

Dog 135.—Injections were given as for dog 123. Moderately severe arthritis developed, which clinically and at autopsy was worse on the treated side. Culture



of the treated left knee yielded nonhemolytic *Staph. aureus*; culture of the right knee showed no growth after seventy-two hours. The dog was killed on the seventh day.

Dog 136.—Injections were made as for dog 123. The dog became very ill; a severe lesion developed in both knees, the lesion in the left being more severe. At autopsy on the ninth day the right (control) knee contained 2 cc. of pus; the left knee contained 5 cc. in the joint and 15 cc. in an abscess which had burrowed into the leg. The organism was recovered from both knees.

*Summary.*—In sixteen dogs the right knee was given an injection of 300,000,000 staphylococci suspended in broth, and the left knee simultaneously received an injection of the same number of bacteria suspended in bacteriophage. In every control knee there developed well marked suppurative arthritis; in no case did the bacteriophage completely protect the left knee against the formation of arthritis, but in eight (50 per cent) of the dogs the treated knee showed less severe damage than the control. In two dogs the knees were damaged equally, and in six the treated knee was worse, clinically or pathologically or both, than the control. Culture of the control knee was positive for *Staph. aureus* in twelve cases and sterile in four; eight cultures of the left, or treated, knees yielded *Staph. aureus*, and eight were sterile. In none of the treated knees could bacteriophage be recovered at autopsy. In four controls and four treated knees the staphylococcus recovered at autopsy had lost its hemolytic power. The sixteen experiments of this series were allowed to run for varying lengths of time from one to thirty-two days. The effect of the bacteriophage did not seem to vary consistently with the duration of the infection. In this series, no bacteriophage treatments were given after the original injections.

Table 1 shows the results of this series in condensed form:

TABLE 1.—*Results of Experiments in Series IV*

Dog	Duration of Experiment, Days	Condition of Treated Joint Compared with Control	Culture of Treated Knee at Autopsy	Culture of Control Knee	Serum Antiphage
116	11	Worse	Negative	Negative	Strong
117	8	Better	Negative	Positive	Weak
118	1	Slightly better	Negative	Positive	Strong
119	18	Better	Negative	Positive	Strong
88	22	Worse	Positive	Positive	Moderate
103	28	Same	Positive	Positive	Moderate
112	32	Same	Negative	Negative	Moderate
122	15	Slightly better	Negative	Positive	Moderate
123	18	Better	Negative	Positive	Strong
124	21	Worse	Positive	Positive	Strong
125	20	Slightly better	Negative	Negative	Strong
126	21	Better	Positive	Positive	Strong
133	5	Better	Positive	Positive	Weak
134	5	Worse	Positive	Positive	Weak
135	7	Worse	Positive	Negative	Moderate
136	9	Worse	Positive	Positive	Weak

These results were not encouraging. The bacteriophage used for the aforementioned animals, although causing four plus lysis grossly

in tubes of broth, often showed a few colonies of staphylococci when plated on agar before filtration. It was therefore possible that the poor results were due to less than maximum potency of the bacteriophage. The method of preparation of the phage was therefore changed, and the method employed by the d'Herelle Laboratory in Paris was adopted. The same strain of staphylococcus and the same race of bacteriophage were continued. This method of preparation resulted in a phage of maximum potency which not only gave four plus lysis in broth tubes but showed no growth on agar plates before filtration. Any lot failing to meet these specifications was discarded. With this new phage of maximum potency it was decided to repeat the experiment on a short series of dogs.

#### SERIES V

Four dogs were given injections similar to those used for series IV, but a bacteriophage of greater potency was employed.

Dog 220.—Three hundred million bacteria (Staph. D-4) in 1 cc. of broth were injected into the right knee, and 300,000,000 bacteria (Staph. D-4) in 1 cc. of bacteriophage into the left knee. Severe arthritis developed in both knees, perhaps slightly less severe in the treated knee clinically and at autopsy. On both sides the abscess extended into the leg along the tendon of the extensor digitorum muscle. Culture of both knees yielded hemolytic Staph. aureus. The dog was severely ill and was killed with chloroform on the eighth day.

Dog 221.—Injections were made as for dog 220. A moderately severe lesion developed which was clinically about the same on each side but at autopsy much worse in the treated left knee. The animal was killed on the seventh day. Cultures of the right knee yielded nonhemolytic Staph. aureus; that of the left knee, large gram-positive bacilli (contamination).

Dog 222.—Injections were made as for dog 220. A fairly severe lesion developed in both knees; clinically it was about equal in the two knees, but at autopsy the treated knee showed less damage than the control. The animal was killed with chloroform after forty-eight hours. The organism was recovered from both knees.

Dog 223.—Injections were made as for dog 220. Very mild and transient arthritis developed, from which the dog recovered on the fourth day. On the sixth day distemper developed. The animal was killed with chloroform on the seventh day. At autopsy the control knee showed very little change from the normal, whereas the left knee presented a well defined purulent synovitis. Cultures of the right knee showed no growth; that of the left knee, nonhemolytic Staph. aureus and gram-positive bacilli.

*Summary.*—In two of four dogs, the treated knee was less severely damaged than the control, and in two it was more severely damaged—about the same percentage as in series IV.

Apparently, therefore, it is not the impotence of the bacteriophage which accounts for the failure of the treatments, and one is forced to the conclusion that in a closed synovial cavity this substance will not protect against infection, even though the bacteria are completely

susceptible to the phage in vitro and though the phage is injected into the joint simultaneously with the bacteria. Obviously there was no use of conducting further experiments in which conditions would more nearly approach human clinical conditions. However, as a matter of theoretical interest it was decided to try the effect of injecting a bacteria-bacteriophage mixture into dogs' knees at varying lengths of time after the bacteria and bacteriophage had been in contact in the test tube at 37 C., thus allowing time for the fixation of the bacteriophage corpuscles by the bacteria (if that is the mechanism of bacteriophagy).

#### SERIES VI

Four dogs were used. The right knee was used as a control, and no anesthesia was used. The bacteria were from an eighteen hour agar slant of Staph. D-220 (recovered from the right knee of dog 220, series V), washed down with 1 cc. of broth; 2 drops of this heavy suspension was then added to 8 cc. of broth, giving a turbidity of 500,000,000 bacteria per cubic centimeter. This suspension was then divided, half being used for the control injections and the other half mixed with 0.2 cc. of bacteriophage, incubated and used for injections into the left knee.

Dog 248.—Two hundred and fifty million bacteria (Staph. D-220) in 0.5 cc. of broth were injected into the right knee, and 0.5 cc. of the bacteria-bacteriophage mixture (also containing 250,000,000 bacteria [Staph. D-220]) after twenty-five minutes' incubation, into the left knee. Moderately severe arthritis developed in both joints, but the left knee was slightly less damaged than the control both clinically and pathologically. The dog was killed on the seventh day. The condition in both knees was subsiding at that time. Cultures of both joints yielded nonhemolytic Staph. aureus, that of the left knee showing no contamination with bacteriophage.

Dog 249.—Injections were made as for dog 248, the bacteria-bacteriophage mixture having been incubated for twenty minutes. The left knee was clinically and pathologically much more damaged than the right, which showed very little inflammation at autopsy. Culture of the right knee showed no growth; that of the left showed nonhemolytic Staph. aureus not contaminated with phage. The animal was killed on the ninth day.

Dog 250.—Injections were made as for dog 248, the bacteria-bacteriophage mixture having been incubated for thirty-four minutes before injection. A severe bilateral lesion with marked general reaction developed. Clinically and at autopsy one knee was as bad as the other. The organism was recovered from both joints when they were opened on the seventh day.

Dog 251.—Injections were made as for dog 248, but after thirty-eight minutes' incubation. The dog showed no reaction to the inoculations, and no arthritis developed in either knee. The animal was saved for use in another experiment. There was no autopsy.

*Summary.*—Of four dogs which received injections as described, one showed a high resistance, and no arthritis developed in either knee; in one the treated knee was less damaged than the control; in another it was more damaged than the control, and in the fourth animal no difference could be seen between the two joints either clinically or

at autopsy. Apparently thirty minutes is not enough time for the "fixation" of staphylococci by the virulent bacteriophage. The organism was recovered from the left knee in all three cases in which cultures were taken, and in the case of one control knee the culture yielded no organism. Table 2 shows briefly the results of the experiments in series V and VI:

TABLE 2.—*Results of Experiments in Series V and VI*

Dog	Duration of Experiment, Days	Condition of Treated Joint Compared with Control	Culture of Treated Knee at Autopsy	Culture of Control Knee
220	8	Better	Positive	Positive
221	7	Worse	Contaminated	Positive
222	2	Slightly better	Positive	Positive
223	7	Worse	Positive	Negative
248	7	Better	Positive	Positive
249	9	Worse	Positive	Negative
250	7	Same	Positive	Positive
251		No arthritis developed	No cultures taken	

#### COMMENT

*Variation in the Resistance to Infection.*—Human synovial membrane is known to have considerable resistance to infection. It is natural to expect this tissue in the dog to show the same property, and it would be unusual if there were not individual variations in the degree of this resistance. As a species, however, it is certain that this animal is less susceptible to staphylococcic infections than is man. That it is not the dog's serum which alone is responsible for this is suggested by the fact that the serum of all dogs of series I, III and IV (twenty-four dogs) was tested for its power to inhibit the growth of the staphylococcus used in the particular experiment, and in no case was there failure of the bacteria to grow in the tube containing the serum as well as, or better than, in the control tube of plain broth. In vitro, at least, therefore, the dog's serum cannot explain the variations in the resistance to infection which were noted. The complication of distemper seemed also to have no effect on the resistance to the infection of the joint. All the dogs were healthy before the experiments began, and it was found to be impossible to predict which dogs would be most susceptible.

*Response of the Normal Joint to Injections of Broth and of Bacteriophage.*—It was apparent from the results in series II, when the pathologic condition of each knee was judged at autopsy, that the effect of broth and of bacteriophage alone in the joints could be ignored. Only in the treated knees of the dogs of series III could these factors have played any part, and in those it was probably the trauma from repeated distention by the treatments with bacteriophage which caused the joints to be more damaged than the controls.

*Results of Treatments.*—Each time an injection of staphylococci and bacteriophage was made, a similar mixture of the same materials was incubated in the test tube as a control. In every instance the control in vitro showed complete lysis, whereas in the animal's knee no such lysis could have taken place, as was shown by the development of a more or less severe purulent arthritis in every case. Why does this striking difference in behavior occur? The complete discussion of the problem is beyond the scope of this paper, but there are two factors which should be considered: the effect of joint fluid and the effect of serum on bacteriophagy.

It was noted in the cases of dogs 287 and 288, series II, that large injections of bacteriophage into the knee were rapidly absorbed and that when some of the fluid could be recovered by aspiration it was found to have lost, or nearly lost, its lytic action after a relatively short period of contact with the interior of the joint. As normal fluid from the joint could not be obtained in quantities large enough to test in vitro, this was the only method available for determining the effect of joint fluid on the action of bacteriophage. Unfortunately, it is not a satisfactory method, since the phage comes into contact with several things in addition to the joint fluid. The fact that the aspirated fluid showed no lytic action or a very weak one suggests that the bacteriophage, injected simultaneously with the bacteria, was quickly inactivated by the joint fluid or the exudate or both, in the experimental joints, thus leaving the bacteria to wreak their havoc almost unhindered. Whatever the effect of bacteriophage on bacteria in vivo, whether lysis or some other attribute is the chief factor in this effect, the inactivation by the fluids of the body exerts the same inhibiting influence.

*The Question of Serum Antiphages.*—The serum of twenty-four of these dogs was tested for the presence of the staphylococcus antiphage before any experimental work was begun on them. It was not considered necessary to test for the streptococcus antiphage. The term "antiphage" in this connection is misleading, since it suggests an antibody produced in the blood stream in response to the presence of an antigen; in these young dogs which had never received bacteriophage and in which there had never been an infection in which spontaneous staphylococcus phages might have appeared, there is obviously no reason to expect the presence of an antibody to bacteriophage, or antiphage. The fact that dog 2, series II, showed no increase in the strength of his serum "antiphage" after ten injections of bacteriophage over a period of ninety days strongly suggests that "serum antiphage" is simply the inhibiting action of normal serum. Nevertheless, "antiphage" tests were done on twenty-four dogs, both by the Rosenthal method and by a method used by Zaytseff-Jern, in which two tubes are set up, one, the control, containing bacteria plus bacteriophage in broth, and the

other containing the same amount of bacteria and phage with the addition of 2 drops of the serum to be tested. The latter method approaches much more nearly to in vivo conditions than does the Rosenthal test, direct or indirect. The results of the antiphage tests are shown in table 3. Unless otherwise stated, serums were not more than twenty-four hours old when tested.

TABLE 3.—Results of the Antiphage Tests for Various Dogs

Dog	Antiphage by Method of Zaytseff-Jern	Antiphage by Method of Rosenthal	
		Direct	Indirect
1.....	Strong	Moderate	Strong
2.....	Moderate	Weak	Weak
3.....	Very strong	Strong	Strong
4.....	Moderate	Strong	Weak
990*	Moderate	Strong	Weak
79.....	Very strong	Moderate	Weak
80.....	Very strong	Moderate	Weak
81†.....	Very strong	Absent	Absent
82.....	Very strong	Moderate	Weak
116.....	Very strong	Strong	Moderate
118.....	Very strong	Strong	Strong
119.....	Very strong	Strong	Strong
88.....	Moderate	Strong	Weak
108.....	Moderate	Strong	Moderate
112.....	Moderate	Strong	Moderate
122.....	Moderate	Strong	Weak
123.....	Very strong	Very strong	Very strong
124.....	Strong	Very strong	Strong
125.....	Very strong	Very strong	Strong
126.....	Very strong	Very strong	Strong
133.....	Moderate	Strong	Weak
134.....	Weak	Very strong	Weak
135.....	Moderate	Very strong	Weak
136.....	Weak	Strong	Weak

\* This dog not used in the experiments.

† This serum was four days old when tested.

Table 3 is especially interesting when compared with table 1, which shows the results of treatment in the dogs of series IV. It is obvious that the results of the treatments do not coincide with the strength of the animal's antiphage; of seven dogs with strong antiphage reactions, five showed improvement in the treated knee, while two showed exacerbation of the infection in the treated knee; in four dogs with weak antiphage, the treated knee was better than the control in two and worse than the control in two. These results are consistent with those observed in human patients by numerous observers, namely, that the best results of treatment are often seen in patients showing the strongest antiphage reactions. Because of this, antiphage tests were not carried out on the animals of series V and VI, and no attempts were made to influence the effect of bacteriophage by such procedures as auto-hemotherapy.

*Pathology.*—The results of the experiments were judged for the most part by the clinical picture and the gross pathologic appearance of the joints at autopsy. Microscopic sections were made of all the knees except four. It was usually possible to tell the character, but not

the extent, of the infection from these sections. In the majority of the knees the inflammatory reaction was an acute one, with more or less leukocytic infiltration, edema and fibroblastic organization. In quite a few of the knees, however, notably in dogs 80, 81, 108, 116, 123 and 124, the infiltration of the synovial membrane and subsynovial tissues was more of the chronic inflammatory type, the cells being mostly plasma cells, large wandering cells and lymphocytes. Some of the areas in these sections had an appearance quite similar to that seen in human chronic proliferative synovitis. The not infrequent perivascular grouping of the plasma cells and the lymphocytes formed pictures not greatly unlike those of the Aschoff bodies in rheumatic fever. It was found, as might be expected, that the chronic type of inflammatory reaction was seen in the sections from the dogs in which the infection had more or less subsided before autopsy.

*Bacteriology.*—The failure to recover the organism from several control knees can be attributed to the culture medium in two cases of series IV; a check-up of the hydrogen ion concentration of the broth showed that one lot which was being used was too alkaline. In a few other cases it may have been due to the fact that the specimens lay in the refrigerator for twenty-four hours before section and culture. The technic of taking the cultures was the same in all cases. The fact that the bacteriophage was not often recovered from the treated knee at autopsy is not surprising after the results of the experiments in dogs 287 and 288. This test was not made in all the treated knees, and in the two cases in which a weak phage was demonstrated this phage was not built up to its original potency. Perhaps if this had been done, a bacteriophage more appropriate for infections of the joints could have been produced. Further research is necessary along this line.

The frequent loss of hemolytic power by the staphylococcus after it had remained in some of the joints was interesting. That the bacteriophage had nothing to do with this loss of power is shown by the fact that it usually occurred in both knees of the same animal and also that it occurred in some of the dogs of series I which received no bacteriophage. There was no consistent relation between the hemolytic power of the organism and the severity of the infection or between the hemolytic power of the organism and the effect of the treatments with the bacteriophage.

#### SUMMARY AND CONCLUSIONS

The literature was reviewed and no work found on the experimental use of bacteriophage in infections of the joints.

In order to test this biologic principle under controlled conditions, six series of dogs were used: series I, consisting of six dogs in which suppurative arthritis of the knee was produced and left untreated to

determine the course of the disease; series II, consisting of four dogs in which the effect of repeated injections of bacteriophage alone and of broth alone were studied; series III, consisting of four dogs in which purulent arthritis was produced in both knees with subsequent repeated injections of bacteriophage into the left knee, the right remaining as a control; series IV, consisting of sixteen dogs, into the right knee of which bacteria suspended in broth were injected and into the left knee of which the same dose of bacteria suspended in bacteriophage was injected; no subsequent bacteriophage treatments were given; series V, consisting of four dogs treated as in series IV but with a more potent bacteriophage; series VI, consisting of four dogs into the left knee of which was injected a bacteria-bacteriophage mixture incubated for varying lengths of time before the injections were made. Bacteria alone were injected into the right knee as a control.

It is believed that the foregoing experiments are sufficient in the number of dogs used and in the fairly consistent results to establish the following facts:

1. Acute suppurative arthritis can be produced in the dog's knee with the staphylococcus, the lesion showing a tendency to subside spontaneously and the duration of the infection varying in different dogs.

2. Repeated injections of bacteriophage alone into the knee joint of a normal dog are not without some danger of the formation of mild acute synovitis.

3. Repeated injections of broth alone into the normal knee cause no such arthritis.

4. Bacteriophage is useless as the sole means of protecting a joint against a closed suppurative arthritis.

5. The failure of bacteriophage to act in such a situation is due to complicated biologic reactions which are not elucidated by this series of experiments but which are probably in great part related to the inactivation of bacteriophage by body fluids.

6. The presence of serum "antiphage" does not exert any deleterious influence on the outcome of such experiments.

Future research must either develop a bacteriophage which will not be inactivated by body fluids and exudates or find a method of treating the body so as to render its fluids innocuous to the bacteriophage. The latter problem has been attacked with partial success by the use of autohemotherapy: the former probably offers the more fruitful field for investigation.



# EFFECT OF DIET ON WEIGHT OF LIVER AND GLYCOGEN CONCENTRATION IN PARTIALLY HEPATECTOMIZED RATS

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Experimental approaches to the study of the physiology of the damaged liver have been made by (1) the use of hepatic poisons, (2) ligation of the radicles to a lobe of the liver, (3) a reduction of hepatic substance after diversion of the portal blood through an Eck fistula and (4) partial hepatectomy. The most practicable experimental approach to the problem would appear to be the last of these procedures, because of the fact that only by this method can damage to the liver in experimental animals and in controls be approximately comparable. In animals subjected to partial hepatectomy two indexes which may be used for studying the function of the damaged liver are regeneration of the liver and storage of glycogen. In addition, the general effect of damage to the liver may be observed by studying the curve for body weight

The present investigation in the field of the physiology of the damaged liver has employed the method of partial hepatectomy and has been limited to a study of the effects of various diets on the experimental animals. The results of this investigation offer a certain possibility of reference to the clinical problem of the patient with presumable diminution of hepatic function.

## REVIEW OF THE LITERATURE

*Regeneration of the Liver.*—After the removal of 75 per cent of the liver of dogs von Meister<sup>1</sup> and Mann and Magath<sup>2</sup> noted that the liver was restored to 80 per cent of its original weight in a period of about eight weeks. Fishbach<sup>3</sup> confirmed this observation and, in addition, presented a morphologic study of the regenerating liver. Higgins

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1. von Meister, V., quoted by Fishbach.<sup>3</sup>

2. Mann, F. C., and Magath, T. B.: *Am. J. Physiol.* **59**:485, 1922.

3. Fishbach, F. G.: A Morphological Study of Regeneration of the Liver After Partial Removal, *Arch. Path.* **7**:955 (June) 1929.

and Anderson<sup>4</sup> were the first to report the regeneration of liver in the rat after partial hepatectomy. These authors studied a large number of adult animals and applied statistical methods to their observations. The average weight of the liver was found to be 3.58 per cent of the body weight. They noted that the weight of the left lateral and median lobes of the liver averaged from 65 to 75 per cent of that of the entire organ. After the removal of these two lobes complete regeneration occurred by from the tenth to the fourteenth day after operation, and regeneration was most rapid on from the third to the fourth day.

*Effect of Diet on Regeneration of the Liver.*—The effect of diet on regeneration of the liver has been studied almost entirely in animals given hepatic poisons. Opie and Alford<sup>5</sup> demonstrated that a carbohydrate diet protected the liver of the rat from necrosis resulting from chloroform and phosphorous poisoning. Graham<sup>6</sup> was the first to show that carbohydrate prevented damage to the liver from chloroform poisoning in young dogs. It was also shown that the glycogen content of the protected liver was relatively high. Moise and Smith<sup>7</sup> fed rats a variety of diets and then damaged the hepatic cells by chloroform. A morphologic study of the livers of these animals showed that on the basis of resistance to toxicity a diet high in protein is better than a diet high in carbohydrate, which in turn is preferable to a stock diet. The stock diet, moreover, produces greater resistance than a diet high in fat. No report has been found dealing with the effect of diet on the regeneration of the liver after partial hepatectomy.

*Effect of Diet on Glycogenesis.*—The literature<sup>8</sup> abounds in references to the relative values of sugars, amino-acids, fats and metabolites as sources of glycogen in the liver. Greisheimer and Johnson<sup>10</sup> and Greisheimer<sup>11</sup> studied the effect of different diets on the deposition of glycogen in the liver of young rats. Their work is not pertinent to the study reported here.

*Factors Affecting Concentration of Glycogen.*—In recent years it has been shown that the interpretation of glycogen concentrations in

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4. Higgins, G. M., and Anderson, R. M.: *Experimental Pathology of the Liver*, Arch. Path. **12**:186 (Aug.) 1931.

5. Opie, E. L., and Alford, L. B.: *The Influence of Diet on Hepatic Necrosis and Toxicity of Chloroform*, J. A. M. A. **62**:895 (March 21) 1914; J. Exper. Med. **21**:1, 1915.

6. Graham, E. A.: J. Exper. Med. **21**:185, 1915.

7. Footnote deleted by the author.

8. Moise, T. F., and Smith, A. H.: J. Exper. Med. **40**:1, 1924.

9. Cori, C. I.: *Physiol. Rev.* **11**:143, 1931.

10. Greisheimer, E. M., and Johnson, O.: *Am. J. Physiol.* **90**:369, 1929; *ibid.* **94**:11, 1930; J. Nutrition **3**:297, 1930.

11. Greisheimer, E. M.: J. Nutrition **4**:411, 1931.

the liver of experimental animals must be made with caution, since the methods of killing experimental animals in common use have been shown to have an effect on the concentration of hepatic glycogen. It has been shown that bleeding,<sup>12</sup> a blow on the head,<sup>9</sup> decapitation<sup>13</sup> and many anesthetics<sup>14</sup> all cause a fall in the amount of glycogen in the liver. Cori and Cori<sup>15</sup> and Deuel and his associates<sup>16</sup> stated that when amytal is given intraperitoneally in doses large enough to produce quick narcosis the the amount of glycogen in the liver is not appreciably reduced in a short period.

In addition it must be remembered that there are wide variations in the glycogen content of the liver of well fed rats taken directly from their cages.<sup>17</sup> In starved rats the amount of glycogen is relatively constant.<sup>18</sup> Furthermore, Deuel and his associates<sup>19</sup> stressed the importance of sex in its relationship to the concentration of glycogen in the liver. Although no differences were observed in well fed animals, starved males showed higher values for the glycogen content of the liver than did the females. Other investigators have confirmed this observation.<sup>20</sup>

#### EXPERIMENTAL PROCEDURE

Rats of Wistar stock served as experimental subjects. After being weaned they were fed a stock diet.<sup>21</sup> A maximum of eight animals were kept in large cages and given food and water ad libitum. When 60 days old these animals were hepatectomized or laparotomized and were immediately given either a stock diet or one high in carbohydrate, high fat, or high protein (table 1). Sixty animals of the same sex were placed on each diet.

12. Palmer, W. W.: *J. Biol. Chem.* **30**:79, 1917.

13. Evans, C. L.; Tsai, C., and Young, F. G.: *J. Physiol.* **73**:81, 1931.

14. Evans, C. L.; Tsai, C., and Young, F. G.: *J. Physiol.* **73**:67, 1931.  
Murphy, G. E., and Young, F. G.: *ibid.* **76**:395, 1932.

15. Cori, C. I., and Cori, G. T.: *J. Biol. Chem.* **85**:275, 1929.

16. Deuel, H. J.; McKay, E. M.; Jewel, P. W.; Gulick, M., and Grunewald, C. F.: *J. Biol. Chem.* **101**:301, 1933.

17. Cori, C. F., and Cori, G. T.: *J. Biol. Chem.* **81**:389, 1929.

18. Miller, M. M., and Lewis, H. B.: *J. Biol. Chem.* **98**:133, 1932. Barbour, A. D.; Chaikoff, I. L.; McCleod, J., and Orr, M. D.: *Am. J. Physiol.* **88**:243, 1927. Cori and Cori.<sup>17</sup>

19. Deuel, H. J.; Gulick, M.; Grunewald, E. F., and Cutler, C. H.: *J. Biol. Chem.* **104**:519, 1934. Gulick, M.; Samuels, L. T., and Deuel, H. J.: *ibid.* **105**:29, 1934.

20. Stöhr, R.: *Ztschr. f. physiol. Chem.* **212**:121, 1932; quoted in *Chem. Abstr.* **27**:124, 1933. Greisheimer.<sup>11</sup>

21. Bal-Ra (obtained from the Valentine Company, of Richmond, Va.) contains: moisture, 9.57 per cent; protein, 29.38 per cent; fat, 5.7 per cent; ash, 9.03 per cent, and carbohydrate, 46.32 per cent.

On the third, seventh, fourteenth, twenty-first and twenty-eighth days after operation eight partially hepatectomized animals, two laparotomized animals used as controls and two on which no operation was performed were killed. The rats were killed when in a well fed condition immediately after removal from the cage, with the exception of two partially hepatectomized rats that were starved for twenty-four hours.

Partial hepatectomy was done with the rats under ether anesthesia. No aseptic precautions were taken. The technic for this operation has been described by Higgins and Anderson.<sup>4</sup> A midline incision was made; the attachments of the left lateral and median lobes of the liver to the diaphragm were freed; a ligature was placed around the pedicle of each lobe, and the lobes were removed. The wound was closed with two layers of silk suture, one in the muscle and peritoneum and one in the skin. The operation lasted about seven minutes.

TABLE 1.—Composition (Expressed in Percentages) of Diets Used in Experiments

	Stock Diet*	Carbohydrate Diet	Fat Diet	Protein Diet
Protein.....	33.13	20‡	30‡	75‡
Fat.....	10.00	..	52‡	10‡
Carbohydrate.....	39.52	66‡	..	..
Salt.....	.....	4‡	4‡	5‡
Yeast.....	†	6	8	6
Cod liver oil.....	†	4	6	4
Moisture.....	9.25	..	..	..
Crude fiber.....	2.70	..	..	..
Bone phosphate of lime.....	6.22	..	..	..
Ash.....	7.20	..	..	..

\* Data relative to the stock diet were furnished by the manufacturer.

† Cod liver oil and yeast are included in the formula.

‡ Meat residue.

§ Corn starch.

¶ Salt mixture (Osborne and Mendell).

‖ Lard.

At the time of death the rats were given 90 mg. of sodium amytal per kilogram of body weight intraperitoneally, and within three or four minutes the abdomen was opened. Two sections of liver were removed immediately for duplicate determinations of glycogen. The animals were killed by bleeding and opening the thorax. The remainder of the liver was removed and weighed. The total weight of the liver was calculated and recorded. In a few instances blood was drawn for van den Bergh determinations.

The surface area was calculated by the formula employed by Lee:<sup>22</sup>  $12.54 \times W^{0.6}$ .

The sections of liver for the determination of glycogen were dropped into a 30 per cent solution of potassium hydroxide; they usually weighed about 0.5 Gm. The interval between the opening of the abdomen and the immersion of the tissue in potassium hydroxide was less than one minute. The glycogen content was determined by the Pflüger method as modified by Somogyi and his associates.<sup>23</sup> The amount of sugar was determined by the Shaffer-Hartmann procedure,<sup>24</sup> using reagents recently described by Shaffer.<sup>25</sup>

22. Lee, M. O.: *Am. J. Physiol.* **89**:24, 1929.

23. Goode, C. A.; Kramer, H., and Somogyi, M.: *J. Biol. Chem.* **100**:485, 1933.

24. Peters, J. P., and Van Slyke, D. D.: *Quantitative Clinical Chemistry*: vol. II. Methods, Baltimore, Williams & Wilkins Company, 1932.

25. Shaffer, P. A., and Somogyi, M.: *J. Biol. Chem.* **100**:695, 1933.

The liver and both kidneys were preserved for microscopic study and analysis of lipids. These microscopic and chemical observations will be presented as a separate study.

### EXPERIMENTAL RESULTS

1. *Effect of Diet on Body Weight in the Control and the Experimental Animal.*—All the partially hepatectomized rats lost weight immediately after operation (tables 2, 3, 4 and 5). However, the ability to regain body weight was determined by the dietary regimen. The greatest increase in weight in the controls on which no operation was performed, in the laparotomized controls and in the partially hepatectomized animals was observed in the animals fed the stock and the high carbohydrate diet; the smallest gain was noted in the animals fed the high fat and the high protein diet; the laparotomized rats used as controls on the high fat diet consistently showed the smallest increment in weight.

The percentage increase of weight in the animals on the stock diet killed twenty-eight days after the beginning of the experiments was not considered because of a discrepancy in age of about fifteen days.

2. *The Effect of Diet on Ratio of the Weight of the Liver.*—The correct index to be used in estimating changes in the weight of the liver must be based on a reliable standard, such as surface area or body weight. A large liver may or may not be indicative of marked regeneration, since it is well known that the weight of this organ and of other organs is determined to a great extent by the size of the animal. Data concerned with the weight of the liver may be best interpreted by using a ratio employing the measurement of the surface area or of the body weight. On account of the increasing tendency to employ the surface area as a constant for reference, the weights of the liver in this study have been expressed in terms of the ratio of the weight of the liver to the surface area. Although the use of the surface area or the body weight in connection with the estimation of the weights of organs is customary in investigative work, it is believed that the quotients obtained in such determinations are not more than approximately accurate as a measure of the regeneration of the liver. In the first days after operation engorgement with blood to an uncertain degree creates a change in the ratio which has no significance as an index of the amount of regeneration. In the same way in the later stages the deposition of fat and glycogen and the proliferation of connective tissue and blood vessels disturb the ratio.

The weight of the liver was increased markedly during the first few days after operation. Although no attempt was made to estimate the amount of liver left at operation, gross examination of the tissue indicated marked engorgement and some increase in size by the third day. The tissue was firm and livid. Seven days after partial hepatectomy the liver was still engorged, and there was a greater increase in size. After this time the liver appeared normal in color.

(a) Stock Diet (table 2): The liver attained its maximum size on the twenty-first day. There was an increase in the ratio of the weight of the liver to the surface area of from 1.77 to 2.59. There was no further increase in this ratio on the twenty-eighth day.

Laparotomy alone had a marked effect on the ratios as compared to those for animals used as controls. The average ratio for the control group was large (3.12) during the earlier days and gradually decreased as the animals grew older (2.47). The differences did not manifest themselves in the laparotomized rats. However, on the twenty-eighth day the ratios were the same (2.4) in the two groups.

TABLE 2.—*Relationship of the Weight of the Liver to the Surface Area in Partially Hepatectomized and in Control Male Rats on a Stock Diet*

No. of Animals	Type of Animals	Age at Operation, Days	Interval After Operation, Days	Body Weight Before Operation, Gm.			Body Weight at Death, Gm.			Weight of Liver Surface Area $\times 100$		
				Min-imum	Max-imum	Average	Min-imum	Max-imum	Average	Min-imum	Max-imum	Average
0	Partially hepatectomized.....	60	3	114	176	168	120	168	151	1.64	1.84	1.77
6	Partially hepatectomized.....	61	7	114	196	172	150	210	179	1.76	2.60	2.11
0	Partially hepatectomized.....	61	14	138	198	169	162	222	192	1.98	2.41	2.25
6	Partially hepatectomized.....	63	21	154	176	165	180	240	216	2.10	2.79	2.59
0	Partially hepatectomized.....	76	28	180	250	230	214	300	271	1.51	2.11	2.54
2	Laparotomized controls.....	60	3	190	192	191	190	198	194	2.57	2.72	2.53
2	Laparotomized controls.....	61	7	162	162	162	178	184	181	2.46	2.72	2.54
2	Laparotomized controls.....	61	14	132	116	139	160	182	171	2.21	2.66	2.44
2	Laparotomized controls.....	63	21	162	176	169	224	218	235	2.92	3.02	2.91
2	Laparotomized controls.....	79	28	190	210	200	214	240	227	2.36	2.54	2.46
2	Controls without operation.....	60	3	150	180	165	161	190	177	2.77	2.96	2.86
2	Controls without operation.....	61	7	162	184	173	200	218	209	3.18	3.19	3.12
2	Controls without operation.....	61	14	182	184	183	220	244	232	2.61	2.78	2.70
2	Controls without operation.....	63	21	130	150	140	170	224	197	2.35	2.86	2.57
2	Controls without operation.....	79	28	212	214	213	244	254	249	2.42	2.55	2.47
2	Starved partially hepatectomized.....	60	3	112	158	150	122	136	129	1.42	1.42	1.42
2	Starved partially hepatectomized.....	82	7	214	230	222	190	194	192	1.63	1.70	1.69
2	Starved partially hepatectomized.....	61	14	146	162	154	160	170	165	1.64	1.69	1.67
2	Starved partially hepatectomized.....	105	21	250	258	244	232	268	250	1.87	2.26	2.07
2	Starved partially hepatectomized.....	79	28	234	238	240	254	266	260	1.81	1.98	1.85

TABLE 3.—Relationship of the Weight of the Liver to the Surface Area in Partially Hepatectomized and in Control Male Rats on a High Carbohydrate Diet

No. of Animals	Type of Animals	Age at Operation, Days	Interval After Operation, Days	Body Weight Before Operation, Gm.			Body Weight at Death, Gm.			Weight of Liver Surface Area × 100		
				Mini- mum	Maxi- mum	Average	Mini- mum	Maxi- mum	Average	Mini- mum	Maxi- mum	Average
6	Partially hepatectomized.....	61	3	120	170	151	110	166	147	1.47	1.87	1.64
5	Partially hepatectomized.....	61	7	134	192	164	130	202	175	1.54	2.08	1.93
6	Partially hepatectomized.....	60	14	144	188	183	178	232	196	2.35	2.76	2.46
6	Partially hepatectomized.....	60	21	114	172	152	151	232	201	1.82	2.15	1.94
6	Partially hepatectomized.....	61	28	162	178	169	224	248	235	2.21	2.91	2.42
2	Laparotomized controls.....	61	3	138	144	141	140	153	149	2.30	2.33	2.26
2	Laparotomized controls.....	61	7	142	154	148	142	178	160	2.18	2.32	2.25
2	Laparotomized controls.....	60	14	134	166	150	162	208	185	2.06	2.72	2.50
2	Laparotomized controls.....	60	21	110	150	130	132	182	157	1.90	2.07	1.92
2	Laparotomized controls.....	61	28	156	180	168	220	278	247	2.45	2.87	2.68
2	Controls without operation.....	61	3	170	222	196	176	210	193	2.46	3.19	2.78
2	Controls without operation.....	61	7	176	210	192	198	248	223	2.42	2.91	2.69
2	Controls without operation.....	60	14	190	214	202	232	232	232	2.27	2.84	2.50
2	Controls without operation.....	60	21	160	172	166	202	236	219	2.35	2.91	2.58
2	Controls without operation.....	61	28	152	156	154	234	250	242	2.30	2.62	2.46
2	Starved partially hepatectomized.....	61	3	132	178	155	118	152	135	1.50	1.87	1.70
2	Starved partially hepatectomized.....	61	7	180	182	181	160	168	164	1.44	1.61	1.53
2	Starved partially hepatectomized.....	60	14	130	166	148	120	154	137	1.55	1.60	1.54
2	Starved partially hepatectomized.....	60	21	180	198	189	180	226	203	1.77	1.95	1.83
2	Starved partially hepatectomized.....	61	28	166	174	170	226	248	237	1.89	2.01	1.95

TABLE 4.—*Relationship of the Weight of the Liver to the Surface Area in Partially Hepatectomized and in Control Female Rats on a High Fat Diet*

No. of Animals	Type of Anheals	Age at Operation, Days	Interval After Operation, Days	Body Weight Before Operation, Gm.			Body Weight at Death, Gm.			Weight of Liver		
				Minl.	Maxl.	Average	Minl.	Maxl.	Average	Surface Area		
				mm	mm	mm	mm	mm	mm	mm	mm	mm
4	Partially hepatectomized.....	61	3	118	110	130	110	142	125	1.53	2.25	1.43
6	Partially hepatectomized.....	61	7	111	140	127	114	170	131	2.06	2.38	2.08
6	Partially hepatectomized.....	67	11	118	131	127	132	151	113	1.80	2.31	2.00
6	Partially hepatectomized.....	62	21	114	130	122	132	150	142	2.18	2.41	2.31
5	Partially hepatectomized.....	62	28	108	118	128	140	188	108	2.30	2.48	2.27
2	Laparotomized controls.....	61	3	136	156	146	138	161	151	2.30	2.41	2.36
2	Laparotomized controls.....	61	7	120	121	122	128	141	130	2.15	2.23	2.14
2	Laparotomized controls.....	67	14	130	132	131	142	154	118	2.08	2.08	2.07
2	Laparotomized controls.....	62	21	110	122	110	111	156	160	2.21	3.30	2.30
2	Laparotomized controls.....	62	28	112	121	118	152	174	161	2.19	2.33	2.26
2	Controls without operation.....	61	3	111	132	123	121	138	131	2.08	2.59	2.20
2	Controls without operation.....	61	7	122	132	127	136	142	139	2.21	2.36	2.17
2	Controls without operation.....	67	11	106	132	119	130	162	119	2.12	2.28	2.20
2	Controls without operation.....	62	21	124	131	127	124	141	131	2.24	2.22	2.22
2	Controls without operation.....	62	28	120	132	120	158	182	170	2.31	2.71	2.53
2	Starved partially hepatectomized.....	61	3	124	156	140	110	140	125	1.05	1.85	1.72
3	Starved partially hepatectomized.....	61	7	123	132	130	114	122	118	2.20	2.40	2.30
2	Starved partially hepatectomized.....	67	11	114	124	119	114	128	120	1.03	1.73	1.68
2	Starved partially hepatectomized.....	62	21	120	122	121	132	146	130	2.11	2.20	1.97
2	Starved partially hepatectomized.....	62	28	110	120	113	122	140	131	1.77	1.90	1.80



In the starved partially hepatectomized rats the ratios were lower than in the corresponding groups of well fed animals. They varied from an average of 1.42 on the third day to 2.07 on the twenty-first day.

(b) High Carbohydrate Diet (table 3): The ratios of the weight of the liver to the surface area in the hepatectomized animals on this diet reached their maximum value (average, 2.46) on the fourteenth day. The lower ratios obtained on the twenty-first day were undoubtedly due to the absence of sufficient food in the cage before death, which was indicated by the empty stomachs of the rats when killed. The average of the values obtained on the twenty-eighth day was slightly lower than the maximum ratio (2.42).

The effect of laparotomy on the ratio was shown on the third and seventh days of the experiment; for example, the values were 2.26 and 2.25 for the laparotomized rats, as compared with 2.78 and 2.69, respectively, for the animals used as controls. The ratios for the laparotomized rats on the twenty-first day were low because of insufficient food in the cage.

In the starved partially hepatectomized rats the ratios were about the same on the third, seventh and fourteenth days.

(c) High Fat Diet (table 4): The ratios of the weight of the liver to the surface area in the partially hepatectomized animals remained unusually constant throughout the entire period of the experiment, despite the marked deposition of fat in the liver. The greatest variations in the average ratios were from 1.93 to 2.31, the smallest value being obtained on the third day and the maximum on the twenty-first day. There was practically no difference in the ratios for the control rats on which no operation was performed and the laparotomized control rats.

The results of starvation in the partially hepatectomized rats are difficult to interpret, since the ratios on the seventh day were higher than those of the animals of the corresponding age which were fed. Furthermore, the ratios were not as low as those noted for the animals on the standard and high carbohydrate diets on which a similar hepatectomy was done.

(d) High Protein Diet (table 5): The ratios for the partially hepatectomized rats were extremely constant throughout the experiment, with maximum variations between 1.91 and 2.31.

The difference in the effect of laparotomy noted in the animals on a stock diet and on a high carbohydrate diet was not evident in the rats on the high protein diet.

The effect of starvation was rather marked. It may be said that the ratios apparently decreased more markedly in these rats than in any group studied.

*Effect of Diet on the Glycogen of the Liver of Control Rats on Which No Operation Was Performed and of Partially Hepatectomized Rats* (table 6).—Since engorgement of the liver of the partially hepatectomized rats occurred during the first two periods of this experiment, any interpretation of percentage values cannot be seriously considered. Therefore, the total number of grams of glycogen in the liver was also considered in order to estimate the deposition of this material.

(a) Stock Diet: The percentage concentration of the glycogen of the liver of the control rats without operation decreased with the age of the animal. Despite the uniformity of the results obtained with the two animals in each group used as controls, these values are open to criticism, owing to the small number of rats. The results obtained for the laparotomized rats used as controls tended to be uniform. The effect of this operation again manifests itself in a lower and more constant glycogen concentration in the liver.

TABLE 5.—*Relationship of the Weight of the Liver to the Surface Area in Partially Hepatectomized and in Control Female Rats on a High Protein Diet*

No. of Animals	Type of Animals	Age at Operation, Days	Interval After Operation, Days	Body Weight Before Operation, Gm.			Body Weight at Death, Gm.			Weight of Liver Surface Area $\times 100$	
				Min.	Max.	Average	Min.	Max.	Average	Min.	Max.
				mm	mm	mm	mm	mm	mm	mm	mm
6	Partially hepatectomized.....	66	3	101	126	117	100	121	113	1.83	2.06
6	Partially hepatectomized.....	59	7	114	154	127	118	134	126	1.77	2.82
5	Partially hepatectomized.....	61	11	112	131	125	118	134	130	2.22	2.37
6	Partially hepatectomized.....	65	21	110	142	123	118	162	143	2.17	2.35
6	Partially hepatectomized.....	60	28	102	122	113	122	146	134	2.02	2.38
2	Laparotomized controls.....	66	3	91	126	110	98	130	110	2.20	2.50
2	Laparotomized controls.....	59	7	120	122	121	126	130	128	2.35	2.42
2	Laparotomized controls.....	64	11	116	118	132	142	168	155	2.53	2.69
2	Laparotomized controls.....	65	21	122	142	132	141	150	117	2.43	2.47
2	Laparotomized controls.....	60	28	108	126	117	131	142	138	2.27	2.31
2	Controls with no operation.....	66	3	120	132	126	122	131	128	2.43	2.50
2	Controls with no operation.....	59	7	111	130	122	124	140	122	2.33	2.34
2	Controls with no operation.....	61	11	144	150	117	152	168	160	2.21	2.62
2	Controls with no operation.....	65	21	142	170	156	158	180	169	2.31	2.62
Lost	Controls with no operation.....	60	28	...	...	...	...	...	...	...	...
2	Starved partially hepatectomized.....	66	3	104	120	112	90	110	109	1.16	1.68
2	Starved partially hepatectomized.....	59	7	112	120	116	96	108	102	1.48	1.51
2	Starved partially hepatectomized.....	64	11	116	130	123	120	126	121	1.40	1.56
2	Starved partially hepatectomized.....	66	21	126	140	133	122	130	126	1.78	1.83
2	Starved partially hepatectomized.....	60	28	126	110	133	131	146	140	1.63	1.77

TABLE 6.—Average Values for Glycogen in Well Fed Partially Hepatectomized and in Control Rats

Days After Operation	No. of Animals	Type of Animal	Stock Diet, Males				High Carbohydrate Diet, Males				High Fat Diet, Females				High Protein Diet, Females			
			Glycogen, per Cent		Total Content of Liver, Gm.		Glycogen, per Cent		Total Content of Liver, Gm.		Glycogen, per Cent		Total Content of Liver, Gm.		Glycogen, per Cent		Total Content of Liver, Gm.	
			Mini-mum	Maxi-mum	Average		Mini-mum	Maxi-mum	Average		Mini-mum	Maxi-mum	Average		Mini-mum	Maxi-mum	Average	
3	6	Partially hepatectomized.....	0.28	1.19	0.60	0.028	1.09	2.61	1.85	0.079	0.03	0.39	0.16	0.007	0.30	0.60	0.43	0.018
7	6	Partially hepatectomized.....	0.32	1.87	1.22	0.048	2.21	3.03	2.56**	0.137	0.91	1.63	1.28	0.064	0.62	2.93	1.68	0.086
11	6	Partially hepatectomized.....	1.58	2.55	2.08	0.137	3.63	4.53	3.97	0.290	0.99	1.94	1.33	0.065	1.65	2.59	2.25*	0.118
21	6	Partially hepatectomized.....	1.30	2.54	2.28	0.169	1.49*	2.32*	1.99*	0.117*	1.52	2.31	1.94	0.109	0.65	2.20	1.41	0.080
28	6	Partially hepatectomized.....	1.01	2.35	1.80	0.165	1.66	3.34	2.20	0.176	1.31	1.64	1.33**	0.082	1.09	2.30	1.65	0.088
3	2	Laparotomized controls.....	0.83	1.09	0.91*	0.071	2.57	3.58	3.07	0.176	0.89	1.43	1.66	0.099	1.76	2.06	1.91	0.097
7	2	Laparotomized controls.....	1.89	3.68	2.63	0.189	2.90	3.96	3.43	0.186	1.74	1.77	1.75	0.089	1.78	2.45	2.11	0.117
11	2	Laparotomized controls.....	2.46	3.17	2.81	0.189	3.28	3.83	3.55	0.235	1.24	1.36	1.30	0.067	2.12	2.27	2.20	0.153
21	2	Laparotomized controls.....	2.11	2.53	2.32	0.224	0.70*	1.87*	1.28*	0.064	1.40	1.63	1.51	0.088	2.13	2.20	2.17	0.134
28	2	Laparotomized controls.....	2.46	2.61	2.53	0.202	3.33	3.34	3.34	0.206	1.23	1.26	1.24	0.079	1.98	2.00	1.99	0.112
3	2	Controls without operation....	3.20	3.40	3.30	0.264	2.38	2.67	2.52	0.207	0.86	1.49	1.17	0.063	2.31	2.48	2.40	0.136
7	2	Controls without operation....	3.50	4.39	4.09	0.405	2.38	2.37	2.82	0.245	1.10	2.04	1.57	0.083	2.15	3.15	2.65	0.145
11	2	Controls without operation....	2.60	3.16	2.88	0.256	2.02	2.62	2.32	0.191	1.62	1.71	1.66	0.092	1.30	2.21	1.75	0.113
21	2	Controls without operation....	2.35	2.80	2.57	0.197	2.92	2.97	2.95	0.243	1.25	1.49	1.37	0.072	1.86	1.85	1.80	0.121
28	2	Controls without operation....	1.62	1.63	1.33	0.113	3.47	4.30	3.88	0.323	1.78	2.41	2.09	0.145	+	+	+	+

\* The stomach was empty at the time of death, representing unintentional starvation.  
 \*\* Five animals are represented by this value.  
 + Lost

The total amount of glycogen in the liver of the partially hepatectomized rat gradually increased from an average minimum amount of 0.028 Gm. on the third day to a maximum of 0.169 Gm. on the twenty-first day. It will be noted that this maximum value did not approach the minimum value of 0.189 Gm. (at the end of seven days) for the laparotomized control animals.

(b) High Carbohydrate Diet: There was a definite difference in the glycogen concentrations for control rats on which no operation was performed and the laparotomized control rats. Despite the higher percentage concentration in many of the laparotomized animals, the absolute amount present was smaller in many cases, owing to the smaller livers. The number of grams of glycogen deposited was definitely low in the laparotomized rats killed on the third and seventh days after operation.

The average absolute amount of glycogen in the partially hepatectomized rats increased from 0.079 Gm. on the third day to 0.29 Gm. on the fourteenth day and decreased to 0.176 Gm. on the twenty-eighth day. The highest glycogen concentration (0.079 Gm.) on the third day after operation was seen in rats on this diet. The average maximum value of 0.29 Gm. of glycogen was almost as high as the largest amount deposited in the liver of laparotomized control rats (0.306 Gm.).

The absence of sufficient food and its effect on the glycogen of the liver are markedly demonstrated in these animals. A short period of no ingestion of food resulted in a precipitous drop in the values for glycogen.

(c) High Fat Diet: The lowest percentage and absolute values for glycogen in the entire series of control rats on which no operation was performed and of laparotomized control animals were noted in the control animals fed this diet. Laparotomy has no apparent effect on the values for the glycogen of the liver.

The partially hepatectomized rats also presented exceedingly low values. On the third day after operation there was an almost complete absence of glycogen (0.007 Gm., or 0.16 per cent). The average maximum values of 1.94 per cent and 0.109 Gm. of glycogen were noted on the twenty-first day and were higher than the concentrations for the corresponding control groups.

(d) High Protein Diet: The average values for glycogen for these control animals were somewhat variable. They were relatively low but were definitely higher than those for the rats on the high fat diet.

The values for glycogen for the partially hepatectomized rats were extremely low. The average absolute values increased from 0.018 Gm. on the third day to a maximum of 0.118 Gm. on the fourteenth day. There was a decrease to 0.08 and 0.088 Gm. on the twenty-first and twenty-eighth days, respectively. During these later days the values for glycogen were about the same as those noted for the animals on the high fat diet during a similar experimental period.

*Effect of Starvation on Concentration of Glycogen in Partially Hepatectomized Rats.*—The lowest average percentage and absolute values were observed after starvation in the animals previously fed the high carbohydrate diet. This is further emphasized by the fact that the carbohydrate-fed animals were males. It has been pointed out that starving males have higher values for glycogen than females. The starving females on the high fat and protein diets had the highest glycogen concentrations. This discrepancy in the glycogen content of the liver of rats on various diets is marked and must therefore have physiologic significance.

#### COMMENT

In order to discuss possible practical applications of the data obtained from this study it is essential first to express in condensed form the results of these experiments.

The feeding of a well balanced stock ration was accompanied by the most rapid gain in weight in both the control and the experimental groups. The hepatectomized animals were able to regain their lost weight rapidly; on the twenty-first day they weighed approximately as much as the rats on which simple laparotomy had been performed. The animals on a high carbohydrate diet showed almost as satisfactory a gain in body weight. The animals on the high protein and high fat diets showed a considerably smaller gain in weight than those in either of the other two groups.

Under the conditions of these experiments the highest values for glycogen in the liver of the partially hepatectomized animals were seen also in the animals on the high carbohydrate diet and in those on the stock diet. Storage of glycogen in the rats fed on high protein and high fat diets was minimal.

One of the most striking observations was the effect of the previous diet on the glycogen concentration in the liver of animals starved for twenty-four hours. The lowest values for glycogen observed in the entire series of experiments were obtained in the rats which had been on the high carbohydrate diet, the livers of which were presumably richest in glycogen prior to starvation. It is particularly interesting that even a short period of starvation had the same effect, as shown by the fact that very low values for glycogen in the liver were observed in all the animals in which the stomach was empty at the time of death in spite of the usual feeding on the preceding day (table 6). It is believed that this effect is the result of an excess production of insulin called forth by the previous high intake of carbohydrate.

It is, of course, not known how directly the observations made in these experiments can be carried over to the clinical field and be applied to patients with livers damaged by inflammatory, neoplastic or degenerative processes. The effect of diet on the patient with a damaged liver is of great importance, and there is need for further and more accurate knowledge which can be applied clinically. It is generally believed by clinicians that a high carbohydrate diet is desirable for the patient with a presumably damaged liver, on the basis that the glycogen concentration of the liver should be kept high, a belief summarized by the rather indefinite phrase "protecting the damaged liver." The impression that patients with hepatic disease do better on a high carbohydrate diet is substantiated by repeated clinical experience. Experimental evidence, such as has already been cited in relation to poisonings, etc., has given weight to this conclusion without necessarily explaining the mechanism. If the type of damage to the liver created in these experiments is at all comparable to other types of damage the results of the present study offer further support to the clinical point of view. Certainly, the effect of either the carbohydrate or the stock diet (the second of which may

be compared to a well balanced hospital diet) was more favorable on the experimental animals in regard both to storage of glycogen and to gain in body weight than was either the high fat or the high protein diet.

A second generalization is perhaps also applicable to the patient. The sharp decrease in the glycogen content of the liver after twenty-four hours or less of starvation of the animals fed a high carbohydrate or stock diet may possibly point a clinical moral. For example, it is customary to prepare patients suffering from severe inflammation of the gallbladder for operation by increasing the carbohydrate intake both by mouth and intravenously with the idea of increasing the amount of glycogen in the liver. A fall in the mortality rate in cases of surgical treatment of the gallbladder has certainly followed the general adoption of this procedure. These experiments suggest that an increase in

TABLE 7.—*Values for Glycogen in Partially Hepatectomized Rats Starved for Twenty-Four Hours Before Death*

No. of Animals	Interval After Operation Days	Stock Diet, Males				High Carbohydrate Diet, Males				High Fat Diet, Females				High Protein Diet, Females			
		Glycogen, per Cent			Total Glycogen, Gm.	Glycogen, per Cent			Total Glycogen, Gm.	Glycogen, per Cent			Total Glycogen, Gm.	Glycogen, per Cent			Total Glycogen, Gm.
		Minimum	Maximum	Average		Minimum	Maximum	Average		Minimum	Maximum	Average		Minimum	Maximum	Average	
2	2	0.10	0.37	0.23	0.009	0.09	0.25	0.17	0.007	0.05	0.16	0.10	0.003	0.04	0.07	0.05	0.001
2	7	0.17	0.18	0.17	0.003	0.03	0.06	0.04	0.002	0.23	0.49	0.36	0.015	0.63	0.55	0.78	0.023
2	14	0.11	0.18	0.15	0.007	0.27	0.49	0.35	0.014	0.53	0.55	0.55	0.021	0.24	0.76	0.50	0.017
2	21	0.37	0.48	0.42	0.030	0.17	0.33	0.25	0.014	0.70	0.90	0.80	0.033	0.54	0.59	0.87	0.036
2	28	0.46	0.76	0.61	0.039	0.05	0.15	0.11	0.007	0.35	0.93	0.62	0.027	0.11	0.47	0.25	0.016

carbohydrate intake should be continued actively throughout the pre-operative and immediate postoperative periods. They show that carbohydrate starvation after a diet rich in carbohydrates results in a lower value for the glycogen of the liver than does starvation of the animals to which a lower amount of carbohydrate has been given. In other words, the patient with a damaged liver who undergoes operation should have a continued high carbohydrate intake throughout the critical period. That it is perhaps justifiable to apply these experimental results clinically is suggested by certain preliminary observations on the glycogen of the liver of surgical patients.<sup>26</sup>

#### SUMMARY

A series of rats subjected to partial hepatectomy were compared with control animals, both rats on which no operation was performed and rats subjected to simple laparotomy. These animals were maintained on (1) a well balanced diet, (2) a high carbohydrate diet, (3) a

26. Unpublished results.

high fat diet and (4) a high protein diet. The weight of the animal, the ratio of the weight of the liver to the surface area and the values for glycogen in the liver were determined for all the animals.

Partially hepatectomized rats fed a well balanced diet regain their normal weight twenty-one days after operation. On the carbohydrate diet these animals grow rapidly but do not reach the level of the control animals. The smallest gain in weight is seen in the animals on high fat and high protein diets.

The remnant of liver increases in weight in all the rats, as judged by the ratio of the weight of the liver to the surface area. The greatest increase in the weight of the liver is noticed in the rats on the well balanced and carbohydrate diets. The significance of this ratio has been discussed.

The highest values for glycogen in the liver in the partially hepatectomized rats are seen in the rats fed on high carbohydrate and stock diets.

Glycogen in the liver is reduced to the greatest degree by starvation of the animals which have been on a high carbohydrate diet.

If one can carry over into the clinic experimental observations made on animals subjected to partial hepatectomy, one must conclude that (a) a well balanced or a high carbohydrate diet will best maintain the patient suffering from a damaged liver and (b) sudden starvation in patients previously furnished a rich carbohydrate intake must be avoided on account of the serious depletion of glycogen in the liver which immediately follows cessation of carbohydrate intake.

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## PATHOGENESIS OF FIBRO-ADENOSARCOMA OF THE BREAST

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The study of tumors of the breast has given rise to many controversial points both as to their origin and as to the predisposing factors in their development. This has been especially true in the case of epithelial tumors. On the other hand, those arising from connective tissue and falling into the category of sarcomas have been neglected because of their rarity and also because of the unsettled state regarding their classification. An unusual opportunity is afforded the investigator attempting to elucidate the question of the relationship between the epithelial and the connective tissue elements in neoplasms of the breast by studying the group classified either as adenomas or as adenofibromas. In this group of tumors of the breast, actively proliferating periductal and periacinal fibrous tissue, which differs from the connective tissue elsewhere in the breast, as well as hyperplastic glandular structures, is present.

In this paper we are using the terms adenoma and adenofibroma interchangeably, and we are concerned only with the definitely encapsulated tumor nodules that can be shelled out and that do not necessarily represent areas of abnormal involution. We consider this an important differentiation, as areas of abnormal involution occur in lactating breasts or may be attendant on the cyclic changes occurring during menstruation. It appears to us that such areas do not represent true neoplasms and that adenomas are new growths within the breast. In this connection, it was first observed by Loeb,<sup>1</sup> then by us<sup>2</sup> and more recently by Heiman<sup>3</sup> that spontaneous adenomas from the breasts of white rats

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From the William H. Singer Memorial Research Laboratory of the Allegheny General Hospital.

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1. Loeb, L.: Further Investigations in Transplantation of Tumors, *J. M. Research* 8:44, 1902.

2. Robinson, George H., and Grauer, Robert C.: Transplantable Benign Adenomas in Rats, *Am. J. Cancer* 16:184 (Jan.) 1932.

3. Heiman, Jacob: The Study of Benign Neoplasms of the Rat's Breast, *Am. J. Cancer* 22:497 (Nov.) 1934.



could be transplanted almost indefinitely into succeeding generations. It is our purpose throughout the present article to show that all the changes that were observed in our experimental animals have been observed in human beings.

All the characteristics exhibited by the normal breast can be observed in adenomas of the breast. The normal breast undergoes definite cyclic changes in its appearance during the menstrual cycle very much as does the endometrium.<sup>4</sup> To parallel this observation, Ingleby<sup>5</sup> showed in her study of adenoma of the breast that the same or similar changes occur in the adenoma as occur in the breast proper during the menstrual cycle. We demonstrated, in 1932,<sup>6</sup> that the adenoma of the breast lactated simultaneously with the breast even when the tumor was transplanted at a subcutaneous site distant from all breast tissue. In order to further establish the fact that the lactation in the adenoma was independent of all connection with breast tissue we transplanted several bits taken from adenomas into the peritoneal cavities of several rats. Lactation occurred in the adenomas at the same time that it was established in the breasts of the rats after parturition. We further noted that involution in the adenomas and in the breasts occurred simultaneously after weaning. In some of the adenomas areas of abnormal involution and of cystic hyperplasia, called chronic cystic mastitis, occurred just as in some of the breasts. All of these changes have also been observed in adenomas of the human breast.

In our first communication regarding the transplantability of adenomas of the breast, we concluded, as did Loeb, that no "takes" were secured in male rats. We were mistaken in this conclusion, for growths in male rats were finally secured eighteen months after transplantation. The growths in the males developed more slowly, and the percentage of "takes" was less than in the females. Heiman secured 66 per cent "takes" in females and 33 per cent in males. The character of the growth was also different. In place of an even distribution of epithelial and connective tissue elements or even of a preponderance of glandular structures, we found a tendency toward an overgrowth of the fibrous tissue, with the resulting tendency toward the formation of a fibroma. This same change, which was originally observed in the male rats, became manifest in the female rats, but only after three years of successive transplantation. Finally a pure growth of fibrous tissue was obtained, in which all ducts and acini had been completely replaced

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4. Rosenberg, quoted by Boyd, W.: *Text-Book of Pathology*, Philadelphia, Lea & Febiger, 1932, p. 651.

5. Ingleby, Helen: *Relation of Fibro-Adenoma and Chronic Mastitis to Sexual Cycle Changes in the Breast*, *Arch. Path.* **14**:21 (July) 1932.

6. Grauer, Robert C., and Robinson, George H.: *Lactation in Transplantable Benign Mammary Adenomas in Rats*, *Am. J. Cancer* **16**:191 (Jan.) 1932.

by the overgrowing connective tissue. Thus a pure fibroma was secured from the original adenofibroma. The counterpart of these experimental observations in the production of fibromas from fibro-adenomas was reported in the human subject by Halpert and Dial.<sup>7</sup> They cited the case of a woman 47 years of age who had a nodule removed from the breast three years previously (1927). In 1930 another nodule appeared in the same location, which on removal was observed to be a pericanalicular and intracanalicular adenoma in which there were practically no epithelial elements. Two years later the nodule recurred. A simple



Fig. 1.—An area from a pericanalicular fibro-adenoma of the mammary gland of a rat.

mastectomy was performed, and a tumor 6 cm. in diameter was removed. This proved to be a pure fibroma. The authors concluded that the three tumors arising in this case—the first nodule, the nature of which was not known, the fibro-adenoma and finally the pure fibroma—probably bore no developmental relationship but were independent tumors that arose at different times in the same breast. Our observations on animals and the cases studied subsequently in human beings show that the fibrous

7. Halpert, Béla, and Dial, David L.: Fibroma of the Breast. *Am. J. Path.* 9:905 (Nov.) 1933.

changes in original adenomas are an expression of altered growth rather than successive independent tumor formations.

One of the tumor nodules that had been transplanted for ten generations to successive female rats began to grow rapidly and caused ulceration of the overlying skin as a result of pressure. This tumor had been transplanted eight months previously from a slowly growing fibroma, which was derived from one of the original adenofibromas. This transplanted tumor measured approximately 8 cc. in diameter



Fig. 2.—An area from a tumor nodule of a woman, showing similarity to the tumor of the rat (fig. 1).

and could be shelled away from the surrounding tissue quite easily. It was firm to the touch and was dull red and gray. When sectioned, it presented the typical appearance of the flesh of fish, which is so characteristic of sarcoma. Microscopically the tumor showed all the morphologic characteristics of a rapidly growing fibrosarcoma. It was extremely cellular and contained spindle-shaped cells, in many of which atypical mitotic figures were observed (fig. 6). There were no glandular structures in the tumor; the transformation from the original adenofibroma to a fibrosarcoma was morphologically complete. But, peculiarly, at this point the evidence of malignancy ceased. The tumor was not

invasive, being definitely circumscribed; it did not metastasize to any distant sites; it did not cause the death of the host. We were unable to find similar morphologic malignant changes in the fibromas of our male rats.

It is not essential that the tumors undergo an intermediary transformation to a fibroma in order to produce sarcomatous changes, though this is the common observation. We found one adenofibroma in which successive transplantation failed to cause a loss of the glandular structures but in which sarcomatous changes were observed. In this tumor

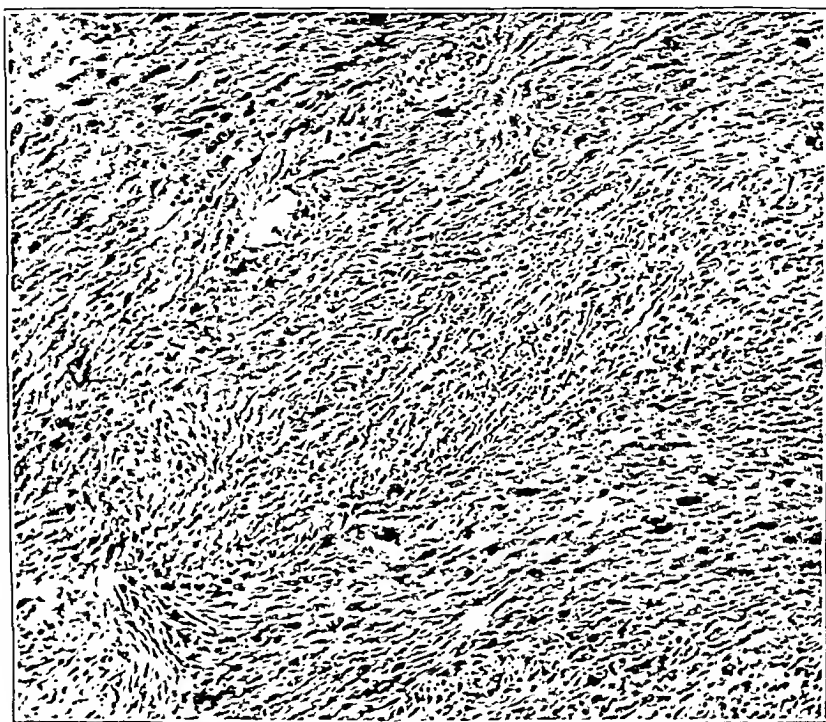


Fig. 3.—Replacement of the glandular structures and the sarcomatous change shown in a mammary tumor of a rat after transplantation for ten generations.

the overgrowing atypical fibroblasts showed progression in such a manner as to "sweep across the section" so to speak, replacing the pre-existing adenomatous structures with highly proliferative and variously sized connective tissue cells (fig. 4). At this stage both adenoma and sarcoma existed simultaneously in the same section.

The tumor nodules that had undergone morphologic sarcomatous changes grew very rapidly after transplantation. Whereas it required from four to six months for a small adenomatous transplant that measured 0.5 cm. in diameter to reach a diameter of 6 cm., a transplant

of the sarcomatous nodule reached the same size in three or four weeks. While none of the tumors growing in male rats has advanced beyond the fibromatous stage up to the present time, transplants of sarcoma from the females to the males have grown with unabated rapidity and have shown the same microscopic pictures as those observed in the same tumors in the female rats.

In view of our experimental observations on sarcomatous changes in adenofibromas of the breast, the work of Sophian<sup>8</sup> is of extreme

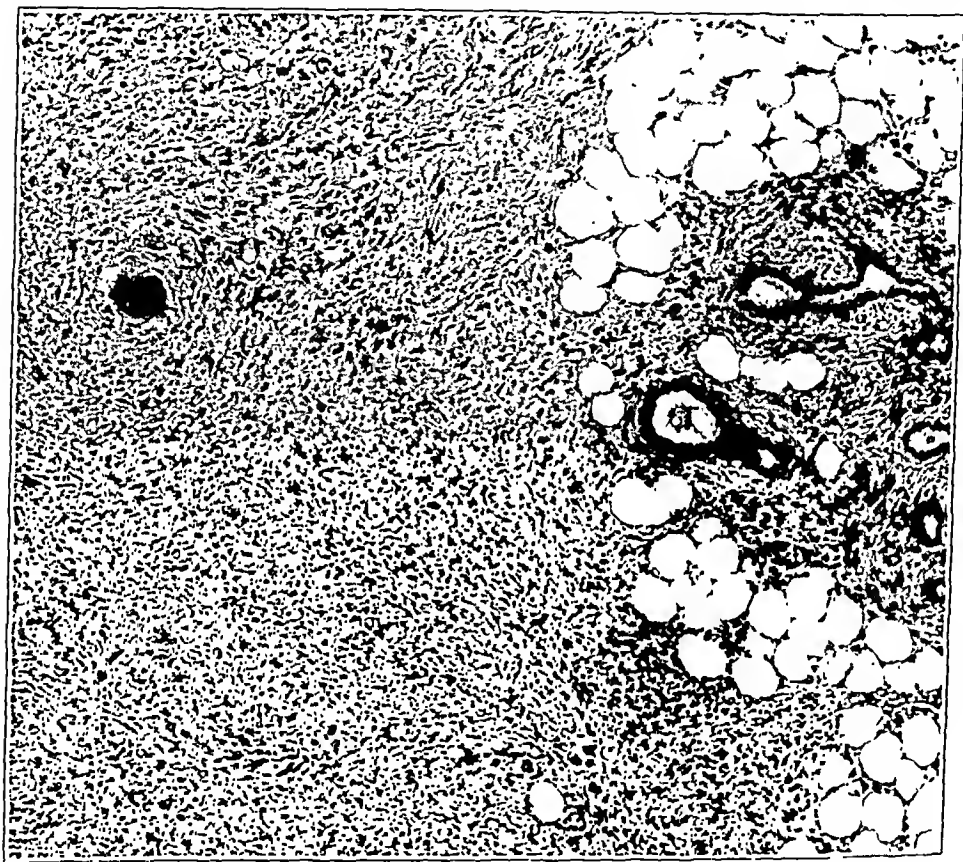


Fig. 4.—Sarcomatous change in a fibro-adenoma of a rat sweeping across the section and replacing the adenomatous structure.

interest. He studied the clinical histories and microscopic sections in fifteen cases of sarcoma of the breast and divided the tumors into two groups; the fibrosarcomas and the adenofibrosarcomas. The latter term was applied to those sarcomas in which epithelium-lined clefts still persisted but in which actively proliferating atypical fibroblasts abounded. He concluded that the adenofibrosarcoma probably arose from a pre-existing adenofibroma and might develop into, or appear in recurrences

8. Sophian, I. H.: Adenofibrosarcoma of Breast. *Arch. Path.* 9:1007 (May) 1930.

as, a pure fibrosarcoma. From six months to seven years after removal of the tumors five of the seven patients with adenofibrosarcoma were free from the disease. There were no metastatic nodules, and the lymph glands were not involved. He made a definite point of the fact that adenofibrosarcoma is a distinct type of sarcoma of the breast, and he accurately suggested its possible origin. All the points emphasized in Sophian's study of cases in human subjects were observed by us in our experimental studies.

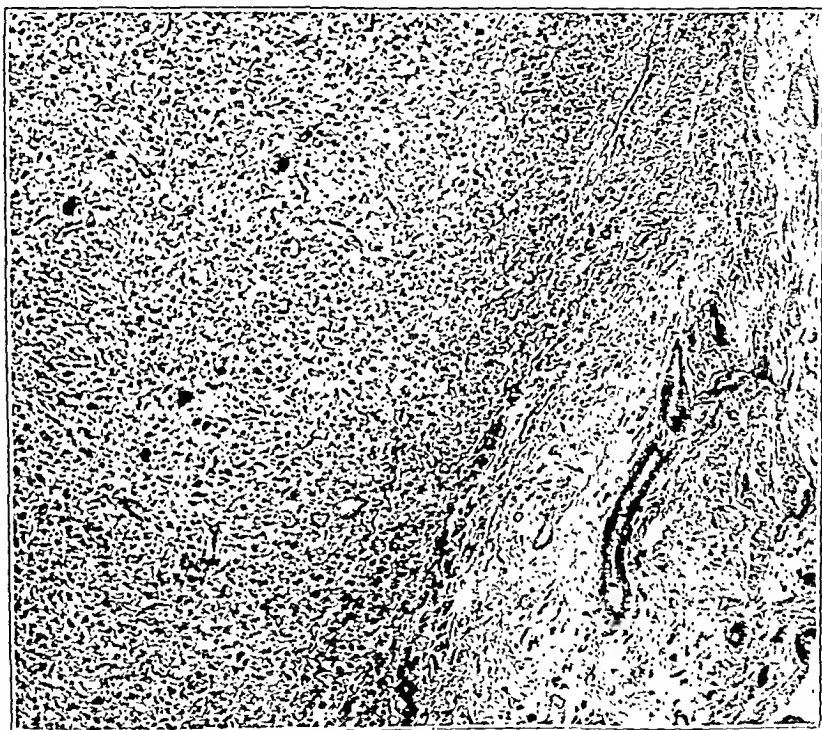


Fig. 5.—Section from a tumor of a human breast, showing change analogous to that seen in figure 4.

We were enabled to study sections of tumors from the breasts of two women and in both cases<sup>9</sup> the microscopic sections were indistinguishable from those of the tumors of our rats:

The first patient was a woman, aged 52 years, who had noticed a lump in the upper right quadrant of her breast only three weeks before consultation. The mass was the size of a walnut, was freely movable beneath the skin and was definitely circumscribed. There was no involvement of the regional axillary

9. Permission to study and report the following two cases was extended to us by Dr. Mortimer Cohen of the Magee Hospital and by Dr. J. P. Griffith and Dr. H. H. Pernar of the Mercy Hospital.

glands. When removed it had the appearance of an adenofibroma. Microscopic sections revealed an intracanalicular fibro-adenoma of the breast, in which there were definite sarcomatous changes in the fibrous tissue. These sections were identical with those observed in the rat in which the glandular elements persisted, though sarcomatous change had occurred in the stroma. If no reference was made to the records, the two tumors could not be distinguished microscopically (figs. 4 and 5).

The second patient was a married woman aged 47. One year previously a small nodule was removed from her breast. This was not available to us for examination. Two months before her present admission to the hospital, the

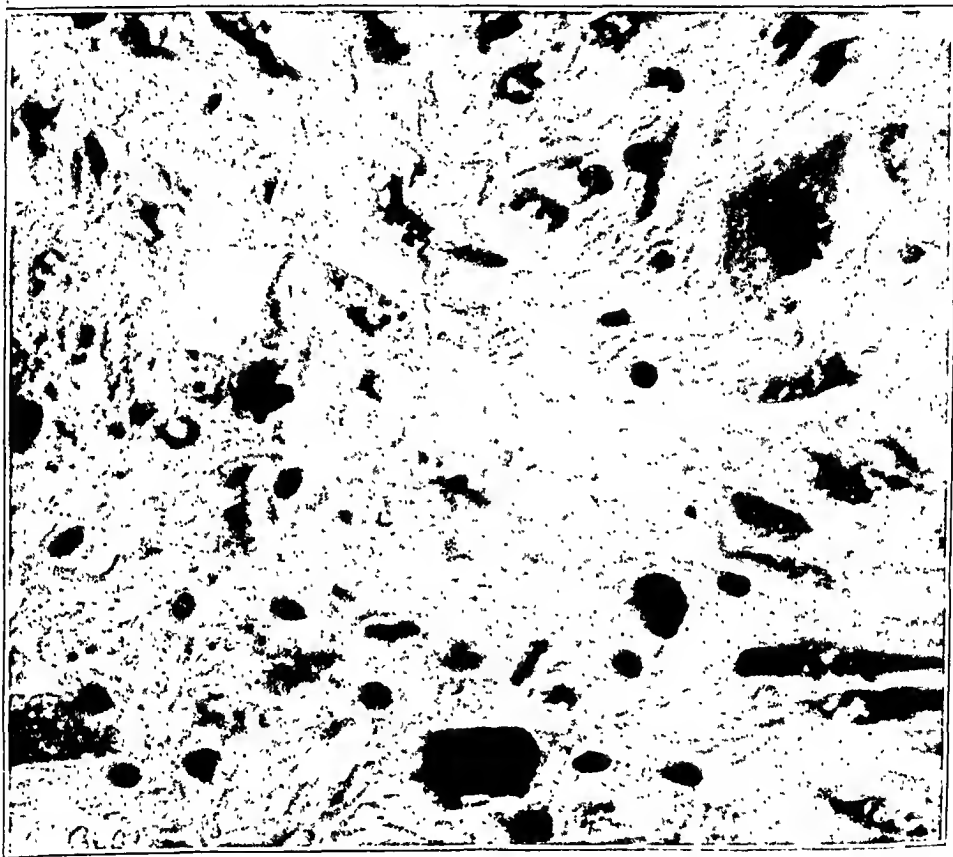


Fig. 6.—High power magnification of a fibro-adenosarcoma of a rat, revealing actively proliferating fibroblasts and numerous atypical mitotic figures.

patient observed that the breast from which the nodule had been removed began to enlarge and that it showed a daily increase in size. The breast at this time was tense, large and fluctuant. Eight hundred cubic centimeters of fluid was aspirated from it. Following this the breast filled again, and simultaneously with the catamenial flow bleeding began from the nipple. Examination of the axilla failed to show any glandular enlargement either on palpation or at operation. The breast was removed by simple mastectomy. The lower portion consisted of a large cyst that was filled with an edematous friable mass resembling coagulated serum and necrotic fat. The wall of the cyst was smooth but showed the presence of a few papillary projections. The microscopic picture in this case proved to be quite interesting. Whereas the transformation of the fibro-adenoma



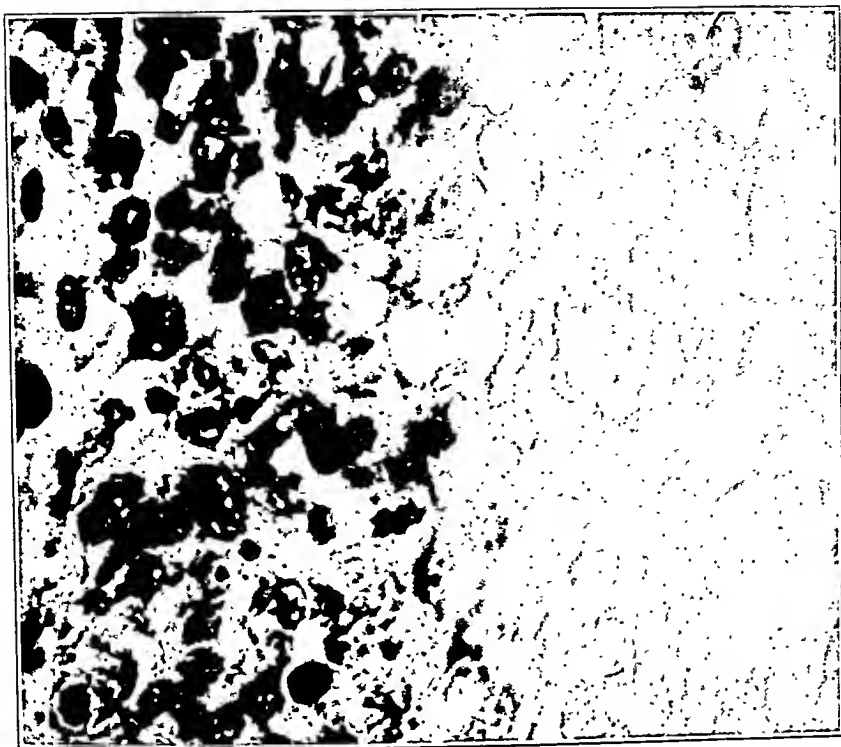


Fig. 7.—High power magnification from a fibro-adenosarcoma of a human breast, showing the same degree of activity as observed in the experimental tumor.



Fig. 8.—A fibro-adenosarcoma of the human breast (second case reported here). The maintenance of the architecture of an intracanalicular fibro-adenoma of the breast may be noted.



to sarcoma was only partially advanced in the first case, it was practically complete in the present instance. That this tumor arose from a preexisting intracanalicular fibro-adenoma could be adduced by a study of its architecture. Several areas of fibrous tissue showed the characteristic arrangement of an intracanalicular fibro-adenoma in which the compressed epithelial slits were still discernible (fig. 8). Other areas showed the persistence of the typical fibrous areas of the adenoma even though these showed early liquefaction necrosis. Those areas that had undergone sarcomatous changes still maintained, in places, the unique infolding and reduplication of the intracanalicular adenoma, with the exception that the fibrous stroma was highly proliferative and contained atypical mitotic figures in



Fig. 9.—Sarcomatous change in the stroma of the fibro-adenoma shown in figure 8.

abundance. The photomicrograph (fig. 8) shows this quite well. All other sections were characteristic of the ordinary rapidly growing fibrosarcoma.

The steady change of this tumor from a definitely benign state to a morphologically malignant one gives warning of its future possibilities. It serves as another link in the strong chain of evidence that all nodules of the breast, without exception, should be excised and investigated.

#### COMMENT

The correlation of our experimental observations with the clinical findings establishes this tumor as a definite clinicopathologic entity and apparently explains the pathogenesis of this type of neoplasm of the

breast. The suggestion that this tumor be considered as adenofibrosarcoma is a logical one, for it is a generic as well as a descriptive term. Although the term sarcoma implies a highly malignant condition which is not observed in this particular tumor, one must necessarily employ it because of the fibrous nature of the tumor. This raises the point concerning the character of the fibrous tissue which is found immediately around the acini and from which it appears that this tumor arises. The periacinal fibrous tissue is of a looser texture and more embryonic in appearance. Owing to some unexplained factors it overgrows the epithelial elements and produces the alterations in the character of the tumor that were observed in the various transplants. It is interesting to speculate on the factors that may influence either connective tissue or epithelial overgrowth, but the known facts are too meager to permit one's arriving at a definite conclusion concerning tissue tension or determining the elements that keep epithelium from overgrowing fibrous tissue and vice versa.

The presence of hormones with tumor growths has been fairly well demonstrated in numerous instances. This has been especially noteworthy in the observations on hydatidiform mole, chorionepithelioma,<sup>10</sup> teratoma<sup>11</sup> of the testis and generalized carcinomatosis.<sup>12</sup> But it appears that with the advent of each new fact more questions arise that demand solution than previously existed. The newer interpretation of the production of various abnormalities of the breast as being an expression of hormonal activity appears logical to us, but we are reluctant to consider a definite neoplasm, such as a fibro-adenoma, as being merely an area of abnormal involution. We consider this especially true since we demonstrated that an adenofibroma of the breast will continue to grow indefinitely during transplantation whereas breast tissue when transplanted exhibits no neoplastic characteristics.

#### CONCLUSIONS

Evidence is advanced to prove the existence of adenofibrosarcoma of the breast as a clinical and pathologic entity.

The mode of development of this tumor from a benign adenoma of the breast to a morphologic sarcoma is followed both in the experimental animal and in the human subject.

Emphasis is placed on the fact that true adenoma of the breast is a neoplasm and not an area of abnormal involution.

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# FIBRO-ADENOMA OF THE BREAST DURING PREGNANCY AND LACTATION

CLARENCE S. MORAN, M.D.

OMAHA

Although little attention has been paid to fibro-adenomas of the breast observed during pregnancy and lactation, a study of these lesions is important since the changes seen are frequently confused with changes due to a malignant condition. Especially is such a study of interest in the light of the hormonal relationship of these lesions to the structure and function of the normal breast.

The term fibro-adenoma denotes an encapsulated fibro-epithelial lesion with either the pericanalicular or the intracanalicular type of connective tissue predominant.<sup>1</sup> Nineteen cases of fibro-adenoma modified by pregnancy, including 9 of lactating adenoma or so-called cystadenoma (Billroth, 1860; Gross, 1879; Power, 1885; Speese, 1909, and others), have been reported in the literature (McFarland, 1922, 1927; Sudler, 1923; Ingleby, 1932; Cheate and Cutler, 1931, and others). Several cases reported before 1900 which might properly belong to this group were rejected because the variance in terminology and the lack of photomicrographs make it impossible to determine the true nature of the growths.

The 27 tumors (table 1) which form the basis for the present study were fibro-adenomas which were removed during pregnancy or lactation or following the cessation of lactation. These tumors were compared with 500 fibro-adenomas excised from menstruating women which were recently reported on by Oliver and Major (1934), the microscopic preparations of which I have since reviewed. A comparison of the two groups is shown in table 2. The pregnancy changes were compared with histologic sections made from human breasts during pregnancy and with numerous preparations from experimental animals, including mice, rats, guinea-pigs, rabbits and monkeys. These animals were pregnant or pseudopregnant or had had pregnancy changes induced by the administration of hormones.

Fibro-adenomas modified by pregnancy or lactation do not differ fundamentally in their clinical features from the tumors of the same type in nonparous females. They occur most frequently in subjects between the ages of 20 and 25, the age incidence ranging from 18 to 40 years. They are apparently most common in white women. At

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1. Pericanalicular lesions are known as *fibromatous* adenomas of the breast, and intracanalicular lesions as *myxomatous* adenomas of the breast.

TABLE 1.—Data on Fibro-Adenomas Removed During Pregnancy and Lactation

Case	Race	Age, Years	Duration	Symptoms	Diameter, Cm.	Site <sup>1</sup>	Relation to Pregnancy and Lactation	Treatment	Type of Tumor	Comments
1	W	22	Years	Lump	1.0	UOQ	1½ mo. preg.	Excision	Fibromatous	Well, 7 yr.
2	W	20	3 mo.	Lump	1.5	UIQ	2 mo. preg.	Excision	Fibromatous, Schimmelbusch	Well, 10 yr.
3	W	20	2 wk.	Lump	...	...	2 mo. preg.	Excision	Fibromatous	Lost
4	W	24	2 mo.	Lump, pain	2.0	UOQ	1 mo. preg.	Excision	Myxomatous	Well, 2 yr.
5	W	25	2 mo.	Lump, pain	1.0	UOQ	3 mo. preg.	Excision	Fibromatous	Lost
6	W	28	18 mo.	Lump, pain	2.5	...	3 mo. preg.	Excision	Myxomatous	Well, 4 yr.
7	W	26	6 mo.	Lump	3.0	...	4 mo. preg.	Excision	Myxomatous	Lost
8	W	19	6 mo.	Lump	2.0	UIQ	4 mo. preg.	Excision	Myxomatous	Well, 6 yr.
9	W	...	...	Lump	2.5	...	6 mo. preg.	Excision	Fibromatous	Well, 11 yr.
10	W	21	3 mo.	Lump	3.0	UIQ	7 mo. preg.	Excision	Fibromatous	Well, 4 yr.
11	W	...	...	Lump	...	...	6 wk. lact.	Excision	Fibromatous	Lost
12	W	23	15 mo.	Lump, pain	3.0	UOQ	5 mo. lact.	Excision	Fibromatous	Lost
13	W	50	...	Lump	1.0	...	5 mo. lact.	Excision	Myxomatous	Lost
14	W	24	14 mo.	Lump	1.5	...	10 mo. lact.	Amputation	Myxomatous	Well, 8 yr.
15	W	21	10 mo.	Lump, pain	2.0	UOQ	10 mo. lact.	Excision	Fibromatous	Well, 25 yr.
16	W	22	...	Lump	1.5	UOQ	End of lact.	Excision	Myxomatous	Lost
17	W	26	19 mo.	Lump	2.5	UIQ	End of lact.	Excision	Fibromatous	Well, 11 yr.
18	W	30	1 mo.	Lump	...	...	5 mo. invol.	Excision	Myxomatous	Well, 4 yr.
19	W	40	...	Lump	1.5	UOQ	6 mo. invol.	Excision	Myxomatous	Lost
20	W	31	6 yr.	Lump	2.5	LIQ	8 mo. invol.	Excision	Fibromatous	Lost
21	W	19	5 yr.	Lump	3.0	UOQ	12 mo. invol.	Excision	Myxomatous	Lost
22	W	28	15 mo.	Lump, pain	1.5	LIQ	15 mo. invol.	Excision	Myxomatous	Lost
23	W	28	5½ yr.	Lump	3.0	UOQ	2 yr. invol.	Excision	Myxomatous	Well, 2 yr.
24	W	37	14 yr.	Lump	1.0	UIQ	2 yr. invol.	Excision	Myxomatous	Well, 10 yr.
25	W	41	...	Lump	...	UOQ	8 yr.	Excision	Cystic disease	Well, 2 yr.
26	W	41	...	Lump	2.0	UOQ	8 yr.	Excision	Cystic disease	Lost
27	W	35	9 yr.	Lump	3.0	...	...	Excision	Fibromatous	Well, 5 yr.; died

1. UOQ indicates upper outer quadrant; UIQ, upper inner quadrant; LOQ, lower outer quadrant; LIQ, lower inner quadrant.

TABLE 2.—Comparison of Fibro-Adenomas Removed During Pregnancy and Lactation with Fibro-Adenomas in General\*

	General Fibro-Adenomas	Fibro-Adenomas During Pregnancy and Lactation
Number of cases.....	500	27
Age at onset.....	20 to 25 yr.	20 to 25 yr.
Race.....	White	White
Duration		
Fibromatous.....	44 mo.	34 mo.
Myxomatous.....	31 mo.	34 mo.
Symptoms		
Lump.....	83%	100%
Pain.....	35%	22%
Location.....	Upper and outer quadrant most frequent	Upper and outer quadrant most frequent
Mobility.....	56%	100%
Multiple.....	15%	7%
Surrounding breast, lumpy.....	5%	7%
Clinically benign.....	94%	97%
Treatment.....	Excision	Excision

1. Summary of 500 cases analyzed by Oliver and Major.

the time of examination the tumors in this series had had an average known duration of thirty-four months. The chief complaint was the presence of a definitely enlarging lump in the breast (27 cases); pain and tenderness were noted in 6 cases and discharge from the nipple in 1 case. One patient (case 12) complained of rapid enlargement of the mass accompanied by pain and tenderness after the onset of lactation. Trauma was recorded in the history in 2 cases.

The physical findings in cases of fibro-adenoma in pregnant or lactating women are also essentially the same as those in the nonparous group. The lesion is located most frequently in the upper and outer quadrant from the midzone to the periphery of the breast and occurs with about equal frequency in the two breasts. The diameter varies from 1 to 16 cm., the average being from 2 to 3 cm.; but size apparently has no relationship to the age of the tumor. The consistency ranges from soft or rubbery to firm. In the group studied all but 1 patient showed a single palpable lump; all the growths were freely movable. There was no retraction of the nipple, dimpling of the skin, atrophy of the subcutaneous fat or enlargement of the axillary glands. In only 1 case (case 14) was there discoloration of the skin and distention of the superficial veins. This tumor was 16 cm. in diameter and occupied the entire breast. All the tumors, therefore, were clinically benign except the last one mentioned, concerning which there was doubt. Although the results of transillumination were not recorded, it is probable that the tumors that were larger than a 25 cent piece would have cast a shadow.

All the tumors were observed to be encapsulated when examined grossly. They varied in shape from round to oval and were smooth in contour. The consistency varied with the degree and amount of pregnancy hypertrophy, the tumor being spongy when the hypertrophy was extensive. One tumor which on palpation was considered to be a single nodule proved to be multiple. Of the tumors that were removed before parturition, 5 showed macroscopic pregnancy changes. On section they were observed to be granular. In the 3 growths in which pregnancy hypertrophy was not seen grossly the nature of the fibrous stroma could be distinguished, being pericanalicular in 1 and intracanalicular in 2. In 2 cases sections only were received. Seventeen tumors were removed during or after lactation. Lactation changes were noted macroscopically, and milk was expressed from 6. Six of the remaining 11 tumors were classified as intracanalicular fibro-adenomas. In 5 cases sections only were received.

#### PREGNANCY CHANGES

Fibro-adenomas are histologically modified by pregnancy and lactation. During pregnancy the microscopic changes correspond in general to those seen in the surrounding normal breast, the chief difference being

in the amount and regularity of the parenchymatous hyperplasia. Epithelial proliferation may be extensive enough to obscure the identity of the tumor, or it may be almost or completely absent. Usually the distribution of the change is very irregular, and large areas of tumor may be apparently unmodified by the pregnancy hyperplasia (fig. 1). Unless the tumor is hyalinized and of long standing, some degree of change is always seen. Multiple tumors in the same breast may show varying

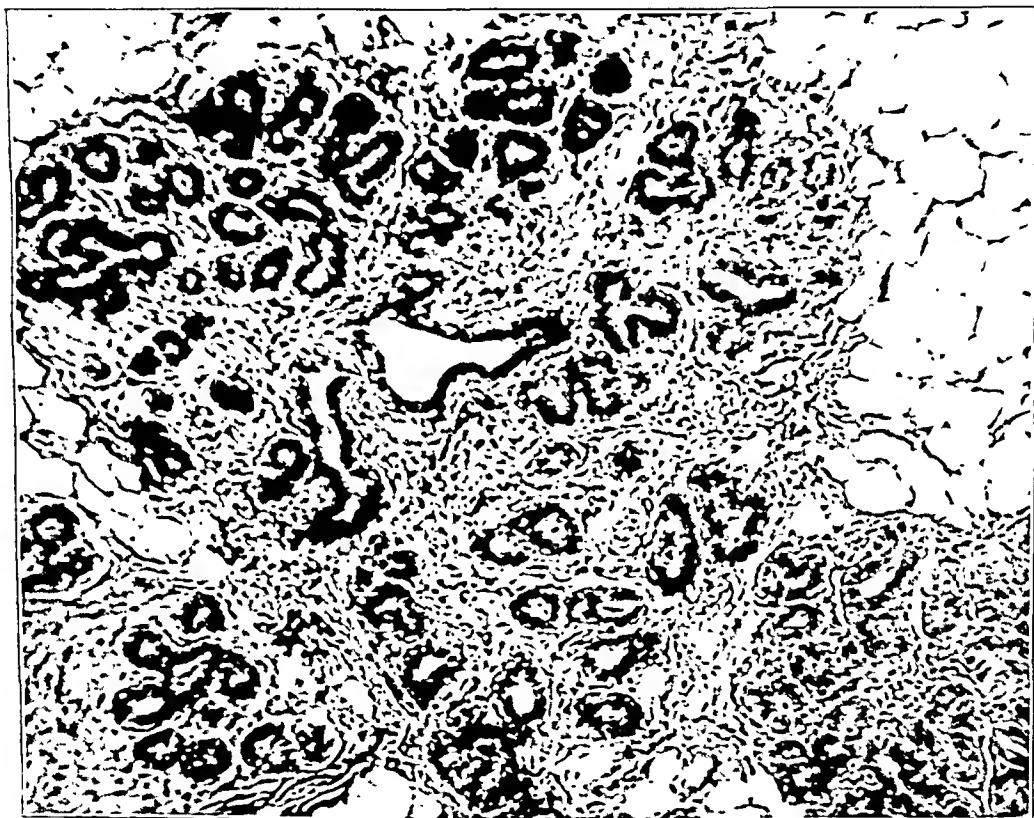


Fig. 1 (case 4).—Photomicrograph showing early and irregular proliferation in the fat of an intracanalicular fibro-adenoma which was removed during the third month of pregnancy. The tumor had been present for two months and was painful and increasing in size.

degrees of response. Although this variability was not observed in any of the tumors of the present series, it was well illustrated by a case reported by McFarland in which the patient had 3 fibro-adenomas in the same breast. The largest tumor showed nearly complete pregnancy hypertrophy, and a smaller tumor showed some change, but practically no hypertrophy was observed in the smallest nodule.

Rosenburg (1922), Ingleby (1932) and others have shown that the normal cyclic changes seen in the breast during menstruation occur also in the fibro-adenomas. In the premenstrual phase the terminal ducts are dilated and epithelium proliferates at the tips. The periductal connective tissue is cellular, pale and edematous.

The premenstrual changes are continued in the first third of the period of pregnancy. The small bulbous sprouts consisting of solid cords of epithelium at the ends of the system of ducts invade the surrounding connective tissue, which is decreasing in amount. These sprouts contain deeply stained cells with vesicular nuclei and numerous mitotic figures. The invading mass is surrounded sometimes by an indistinct basement membrane. As the strands of cells become canalized, the process is repeated; thus the intralobular ducts arise, acini are added and new lobulets (lobule) are formed. As the epithelial changes occur, the amount of periductal and intralobular connective tissue gradually diminishes, suggesting a reciprocal relationship between the parenchyma and its supporting tissue. The fat which is closely associated with the lobule disappears.

Maturing lobulets and proliferating cords of epithelium may be seen in a single microscopic field in the first third of the period of pregnancy. The infiltrating epithelium with its numerous mitotic figures is frequently mistaken for cancer. Such a picture is shown in figure 2. The rate of proliferation however gradually declines, and by the fifth or sixth month (figs. 3 and 4) no proliferative activity can be seen and the lobulets approach maturity. At that time the acini are rounded, and the acinar cells vary in shape from cuboidal to columnar, with their nuclei located near the bases. Also, secretory globules, sometimes seen in the more advanced lobulets as early as the second and third months, begin to appear in the acinar cells. Small amounts of secretion collect in the acini as well as in the ducts, making the intralobular ducts difficult to distinguish from the acini unless examined in serial section. The larger ducts, which are irregular in contour and lined with deeply staining cuboidal or columnar epithelium, may also contain a small amount of secretion. The lining cells, however, show no secretory globules.

During the second half of pregnancy, secretory activity becomes more marked and the blood supply gradually increases. The acini and ducts increase in size and become distended with a secretion containing albumin, various-sized fat globules and so-called colostrum bodies. The secreting cells enlarge and stain less intensely. Their nuclei are compressed toward the basement membrane by the secretory globules, which coalesce in the central end of the cells and cause them to bulge into the lumens of the acini, thus producing lumens of various shapes. As the lobulets increase in size, the connective tissue continues to disappear until before labor the stroma is reduced to thin strands between the

lobulettes and the acini. Since these pregnancy changes are usually irregularly distributed, areas of unaffected tissue may be seen.

Scattered throughout the tumor and near the large ducts are seen rudimentary or refractory lobulettes corresponding to the premenstrual lobulettes seen in all stages of pregnancy and lactation. For some reason these structures have failed to respond to the stimuli of pregnancy. Their presence and number seem roughly in inverse proportion to the number



Fig. 2 (case 5).—Photomicrograph showing early pregnancy change in a fibro-adenoma which might be mistaken for cancer. The patient was white and aged 23. The tumor was removed during the second month of pregnancy. It had been discovered about two months previously. Although the new structures are infiltrating, the cells are of similar size and stain uniformly. An intact basement membrane can be distinguished.

of lactations and are apparently less frequent or even absent in the breasts of multiparous women. Lewis and Geschickter (1934) have suggested that these structures have some relationship to chronic cystic mastitis.



Ten tumors were removed during pregnancy; 6 were pericanalicular and 4 intracanalicular. Pregnancy hypertrophy was noted in 9 cases, in 8 of which there was a history of growth. However, in the remaining case (case 8) there was pregnancy hypertrophy, and the tumor had

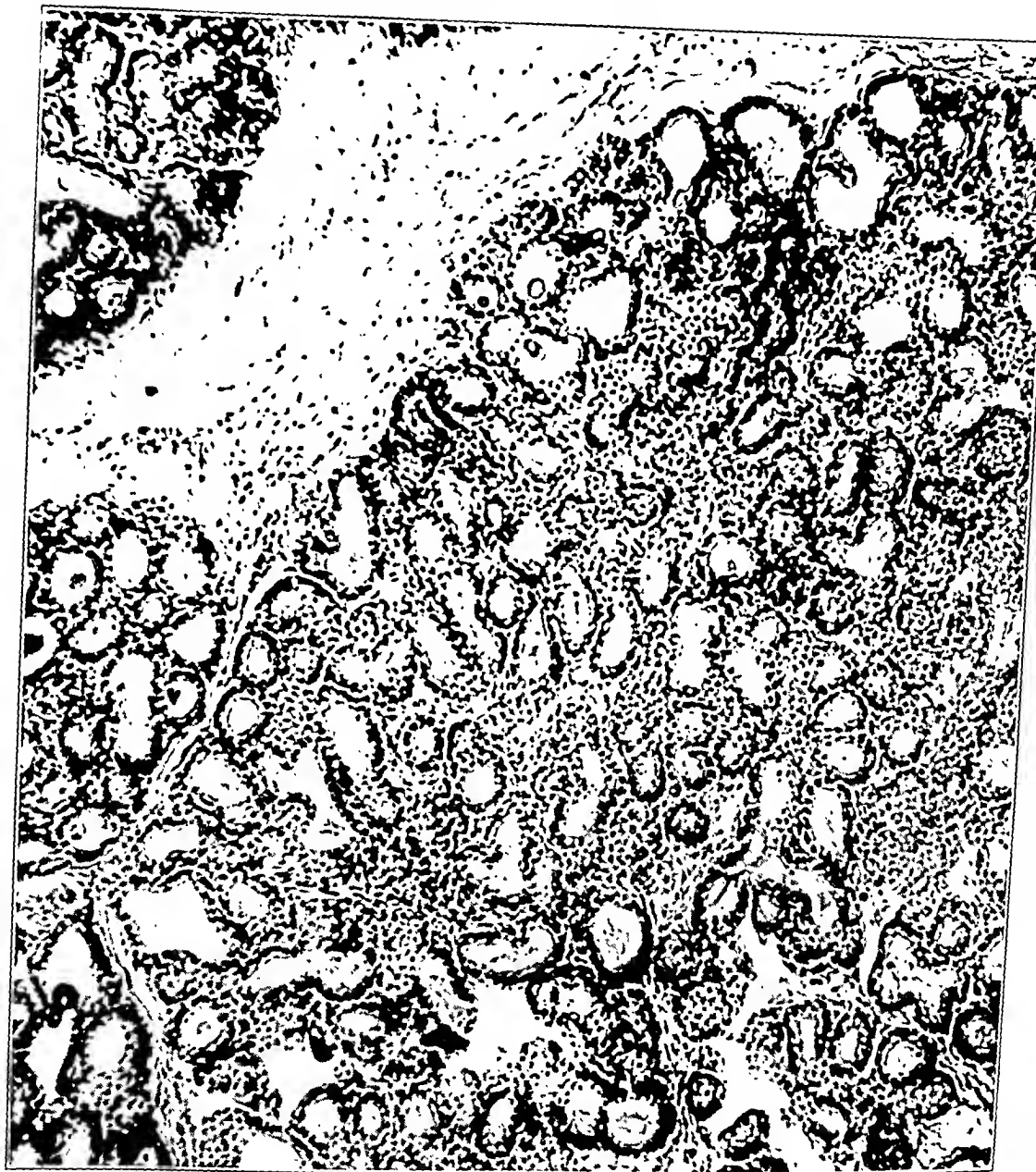


Fig. 3 (case 9).—Photomicrograph showing pregnancy hypertrophy in a pericanalicular fibro-adenoma removed in the sixth month of pregnancy. The distribution of the pregnancy hypertrophy in the tumor is irregular.

therefore probably grown. The pregnancy changes were diffusely distributed in 5 cases and irregularly distributed in 4. In the tenth case (case 1), in which there was no evidence of pregnancy hyperplasia, the tumor had been present for a number of years, and its size had remained

stationary during the previous pregnancy. It was pericanalicular and partially hyalinized.

In each of 2 cases (cases 8 and 10) 2 tumors were found, the sister tumors being identical microscopically.

#### LACTATION CHANGES

During lactation, as in pregnancy, the microscopic picture corresponds with that of the surrounding breast. The ducts and acini are

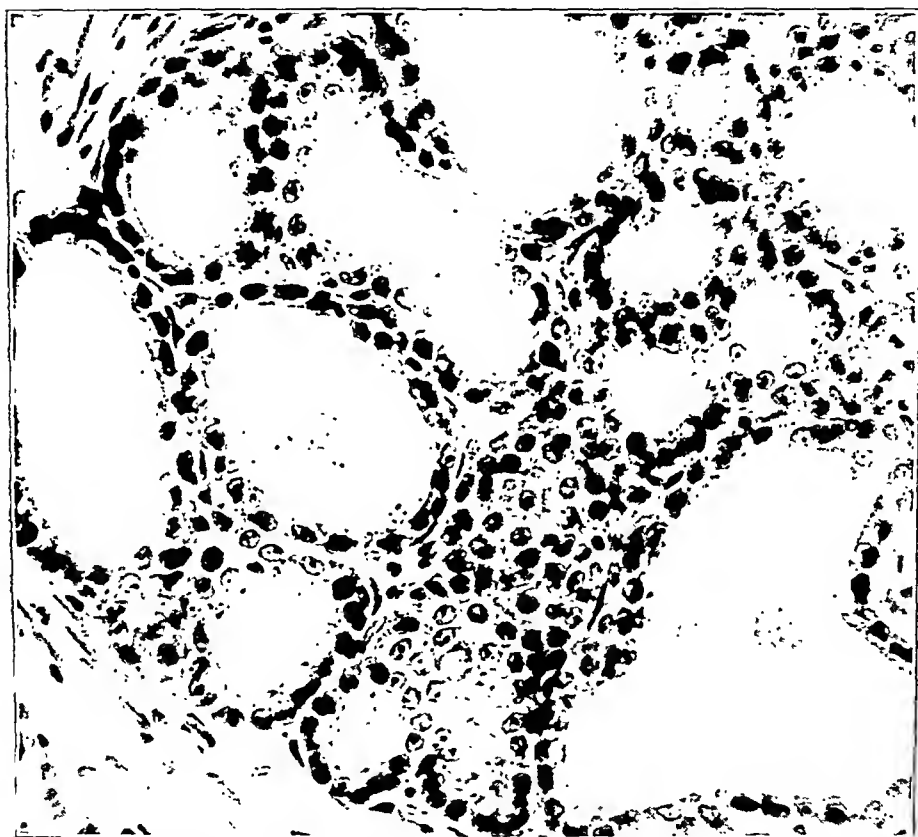


Fig. 4 (case 9).—Photomicrograph showing an area in which the lobulettes are forming, the acini are dilating and secretory activity is beginning.

dilated and filled with secretion. No colostrum bodies are seen. The cells lining the acini are columnar or cuboidal; they stain poorly and are filled with globules of secretion. The lumens are irregular. The intralobular connective tissue is reduced to a minimum. Although numerous lobulettes may be seen secreting, others in the same field are frequently observed in a resting stage, with cells of uniform size and con-

taining very few globules of secretion. Their acinar lumens are narrow and collapsed.

Occasionally during, or more especially near, the onset of lactation a tumor which has enlarged but slightly during pregnancy or has even been unnoticed may enlarge rapidly. If the mass does not diminish in size during nursing, the drainage system has been either cut off or blocked. One such case (case 12) is included in this series. The patient had two children, 18 months and 3 months of age, respectively. The tumor had been noticed for fifteen months. It increased in size but slightly during pregnancy. During the third month of lactation it suddenly enlarged from the size of a walnut to that of a lemon, became tender and painful and required surgical intervention. Microscopically the acini and ducts were markedly distended with secretion. No involution was noted.

Seven tumors (4 pericanalicular and 3 intracanalicular) were removed during or at the end of lactation. On section milk could be expressed from 6. Only 4 had a history of growth, but lactation hypertrophy was noted in all. Some showed beginning involution. The distribution of the change was regular in 3 and irregular in 4.

Involution proceeds as in the normal breast. The acini become smaller, the lining cells atrophy, the amount of secretion diminishes, and finally the lobulettes collapse. Here again the histologic picture may superficially suggest cancer. These changes also occur irregularly, and frequently lactating as well as involuting areas may be seen in a single field (fig. 5). The glandular areas are invaded by phagocytes, and cells loaded with fat (specially stained) can be seen in the various lymphatic channels. Accompanying the parenchymatous changes, the periductal and periacinar connective tissue again proliferates. Gradually the glandular structures are destroyed, the connective tissue is in part restored, and the tumor may resume its nonpregnant state or disappear completely. These changes may be completed in a few months following cessation of lactation but sometimes are delayed for from two to fifteen months (fig. 6).

Occasionally areas of so-called residual lactation persist for years. In one case of the series (case 26, figure 7) a diagnosis of cystadenoma with residual lactation hypertrophy was made. The patient, a white woman aged 41, after nursing her child eight years previously had noted an intermittent milky discharge from the left nipple. About one and one-half years prior to admission she discovered a small lump in the left breast. Physical examination revealed that the ducts beneath the nipple were dilated, and there was a tumor about 2 cm. in diameter in the upper and outer quadrant. Both breasts felt shotty. The mass was excised and macroscopically was identified as a fibro-adenoma. Microscopically the encapsulated tumor showed areas of pericanalicular and

intracanalicular fibro-adenoma, cystic areas and areas which looked like lactation hypertrophy. These areas however were identical with the lobular changes in the adenocystic (Schimmelbusch) type of chronic cystic mastitis. No secretory globules were seen in the cells. The cystic areas were also identical with the small cystic areas seen in cystic disease of the breast.

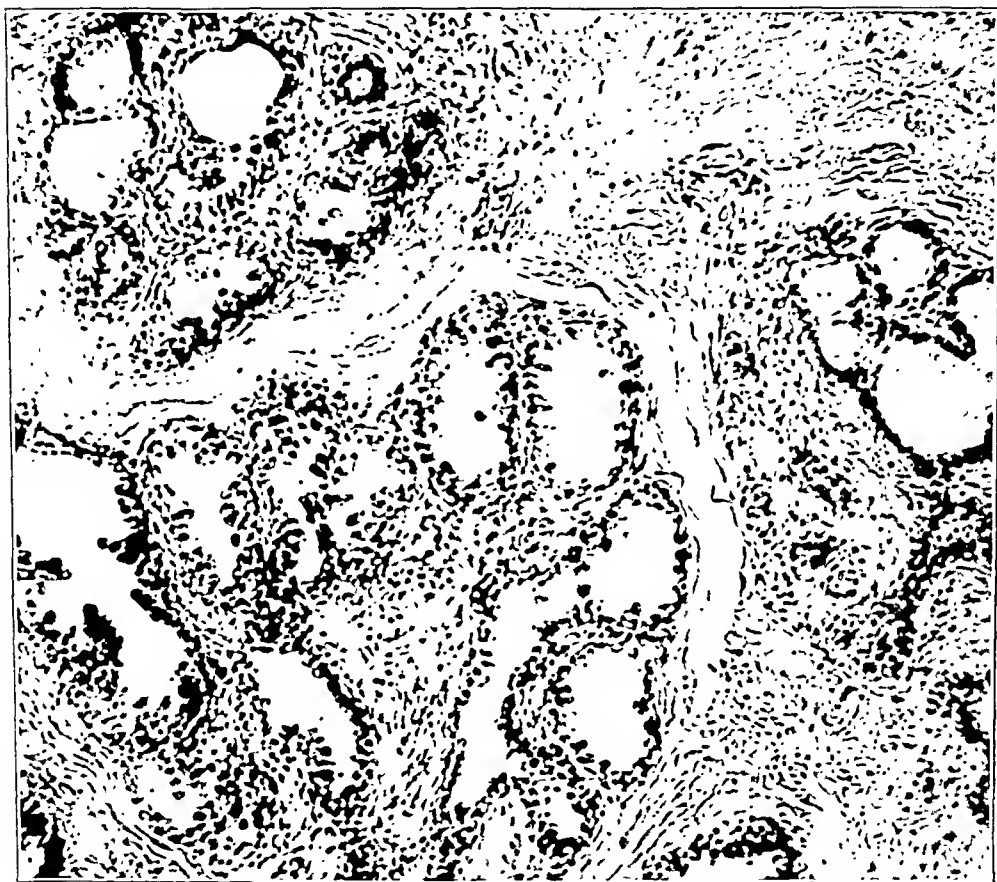


Fig. 5 (case 17).—Photomicrograph showing lactation and involution in a single field of a fibro-adenoma. This tumor, which had been present for thirty months, was excised two months after the infant was weaned. A few dilated acini can be seen. Secretory activity had almost ceased. Involution is marked. The surrounding normal breast presents the same type of change.

In my opinion the changes seen in this tumor, the cystic areas and the so-called residual lactation hypertrophy were probably the result of chronic cystic mastitis. The indefinite history of onset, the intermittent discharge, the dilated ducts beneath the nipple and the presence of chronic cystic mastitis in both breasts support this opinion. No doubt

chronic cystic mastitis is frequently mistaken for cystic fibro-adenoma and residual lactation hypertrophy, and the latter diagnosis should not be accepted until the Schimmelbusch type of chronic cystic mastitis is ruled out. The microscopic picture in cystic disease complicating a fibro-adenoma is shown in figure 8. Lewis and Geschickter have recently shown that chronic cystic mastitis is associated with hormonal disturbances, and since fibro-adenomas respond to the hormones controlling the development and function of the breast, it is reasonable to suppose

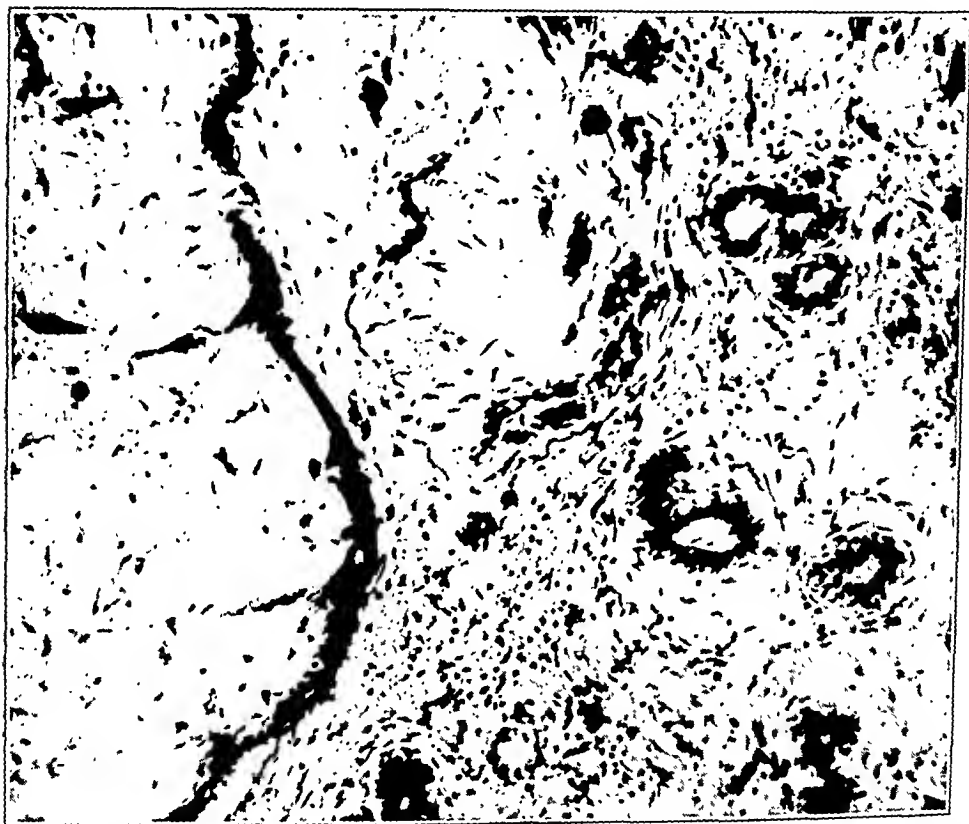


Fig. 6 (case 19).—Photomicrograph of a tumor discovered at the end of lactation. The patient nursed her child for three months. The tumor was removed eleven months later.\* A few intact acini can be seen, but the section is predominately one of involution. The collapsed and atrophic acini are disappearing. Phagocytic activity is marked.

that these lesions also may be involved in the hormonal imbalance responsible for chronic cystic mastitis.

Of the 10 tumors removed after lactation had ceased, 5 were intracanalicular, 2 were pericanalicular and 3 were mixtures of both types. Only 3 had a history of growth during pregnancy. Five showed areas of residual hypertrophy with involution. Two (cases 25 and 26) were interpreted as chronic cystic mastitis complicating fibro-adenoma. No changes were detected in 3. Three tumors had been present during more than one pregnancy. One (case 20) had been present for six

years, and evidence of involution was noted when it was removed eight months following parturition. The tumors in cases 24 and 27 had been present for nine and fourteen years, respectively. In neither was lacta-



Fig. 7 (case 26).—Photomicrograph of so-called residual lactation hypertrophy in a cystadenoma. This tumor was removed eight years after lactation. The patient complained of an intermittent milky discharge and a lump in the breast. The section shows an area of lobular proliferation without secretory activity adjacent to numerous cystic areas.

tion hypertrophy or involution evident, although in the former there was a history of growth during the last pregnancy. Five small tumors

ranging from 0.5 to 1 cm. in diameter were discovered either late in lactation or after lactation had ceased. In each case evidence of lactation hypertrophy could be seen microscopically, indicating that the tumors had been present or had originated during pregnancy but were not discovered until beginning involution.



Fig. 8 (case 2).—Photomicrograph showing chronic cystic mastitis of the Schimmelbusch type in a fibro-adenoma which is beginning to undergo pregnancy hypertrophy. The tumor was removed during the second month of pregnancy.

#### COMMENT

The changes seen in fibro-adenomas during pregnancy and lactation are identical and occur simultaneously with the physiologic changes in the surrounding breast at these periods. Also these changes can be simulated if not actually reproduced in the mammary glands of animals by the administration of the appropriate hormones. It has been clearly demonstrated that the growth and development of the mammary glands in animals are dependent on the estrogenic principle and the progestational

hormone from the corpus luteum. The estrogenic principle controls the growth and development of the nipples and the system of ducts and also sensitizes the ducts to the action of the hormone from the corpus luteum, which is responsible for the development of the lobules (Allen, 1932; Corner, 1929, 1930; Turner, 1931, 1933, and others). The administration of the lactogenic principle from the anterior lobe of the pituitary body to an animal with a mammary gland prepared with the estrogenic principle or with the estrogenic principle and the hormone from the corpus luteum results in the secretion of milk (Stricker and Grüeter, 1929; Corner, 1930; Riddle, 1933; Gardner and Turner, 1935, and others).

Clinically there has long been recognized a relationship between the human breast and the ovary, as demonstrated by the effects of castration and the menopause; by the normal development of the breast at puberty in girls and the rudimentary state of development in boys; by the abnormal mammary development in cases of ovarian tumor in children; by the presence of lobules in the breast only after functional activity of the corpus luteum, and by the cyclic changes which occur in the breast at each menstrual cycle.

The mammary changes produced during pregnancy and lactation are induced by hormones known to be present in high concentration at these times. Aschheim and Zondek (1928) and the Smiths (1934) have shown that the estrogenic principle is present in the blood in gradually increasing amounts during pregnancy in human beings. This is thought to be of placental origin (Allen, 1932). Though there is at present no practical method of detecting the progestational hormone from the corpus luteum in the blood stream, such a hormone is known to be present, and its effects are demonstrated both in the breast and in the uterus. It is thought to be functionally active at least in the early part of pregnancy, and degenerative changes in this endocrine body are usually not seen before the fifth or sixth month of pregnancy. Opinion, however, is divided as to the duration of function of the corpus luteum. It has been shown by Ask-Upmark (1926), Pratt (1927) and Waldstein (1929) that the corpus luteum can be removed early in pregnancy without causing abortion. This phenomenon indicates that the hormone from the corpus luteum is not long required for the maintenance of pregnancy, but it does not prove that this hormone is nonessential for complete mammary development. It is also possible that the secretion of this hormone is taken over, as in the case of estrogenic principle, by another organ, namely, the placenta. The hormone from the corpus luteum has recently been demonstrated to be present in the placenta at full term by Adler, De Fremery and Tausk (1934), but as yet it has not been determined whether it is secreted or only stored there.



The milk-stimulating hormone of the anterior lobe of the pituitary body has been shown to be necessary for the secretion of milk in animals. It is also effective in hypophysectomized animals (Riddle, 1933; Collip and his associates, 1933). Although there is little experimental evidence to show the effect of such a hormone in human beings, it is evident that the pituitary body is in some way involved in the process of lactation. This is indicated by certain cases of pituitary tumor in which lactation has been known to last for extended periods (Cushing, 1932). Recent experiments by Kurzrok, Bates, Riddle and Miller (1934) indicate that administration of this hormone of the pituitary gland may be of value in increasing the supply of milk in women with an insufficient amount. While a hormone of the pituitary gland is probably responsible for lactation in human beings as in laboratory animals, there is as yet no definite proof either of its presence or of its necessity in human beings.

Microscopically, mammary development in human beings and that in animals are essentially the same, both depending on the ovary. It has been proved that this control is hormonal in animals. The hormones known to be necessary for the development of mammary glands of animals are present in high concentration in human beings during pregnancy. The "ovarian hormones" have been shown, at least in some instances, to have the same effect in human beings as in animals. This has been demonstrated by replacement therapy and by the experimental production of menstrual periods (Werner and Collier, 1933; and Loeser, 1934) and of hyperplastic endometrium (Schroeder, 1915; Novak, 1924, 1933; Fluhmann, 1931, and others), although little is known of the actual mechanism of the action of these hormones or of the part played by other endocrine glands.

By inference from animal experimentation it may be suggested, therefore, that during the early stage of pregnancy fibro-adenomas of the breast show epithelial proliferation in response to the progestational hormone from the corpus luteum. In later pregnancy an increasing concentration of the estrogenic principle probably produces changes in the fibrous elements. During lactation, distention and secretory activity in the acini are stimulated by a pituitary principle. After removal of these relatively intense hormonal stimuli, involutional changes develop.

#### DIAGNOSIS AND TREATMENT

When a lesion of the breast is presented for diagnosis during pregnancy or lactation, the important question is that of malignancy. Knowledge of the patient's age and the condition revealed by transillumination of the tumor may be of value; but since the majority of lesions seen at that time are single and clinically benign, a biopsy is necessary to establish a diagnosis.

Cancer of the breast arising during pregnancy and lactation is not rare. Kilgore (1923, 1924) estimated that 4.5 per cent of all cancers in persons below the age of 47 occur in the breast during that period. Ninety per cent occur in persons over 30. However, cancer arising in a fibro-adenoma is rare. In a series of 500 cases analyzed by Oliver and Major (1934) and in 250 cases studied by Semb, no cancer was reported. None was observed in this small series. Nevertheless, changes occurring in a fibro-adenoma during pregnancy and lactation are frequently confused with cancer (15 in this series). This difficulty is encountered most frequently during the first three months of pregnancy (fig. 2) and during late involution. In the early stage of pregnancy, though the proliferating structures are infiltrative and mitotic figures are numerous, the process is orderly and produces a definite pattern, the cells are similar in size and stain uniformly, and the new ducts and acini are usually surrounded by a basement membrane. In the late stages of involution the collapse of the lobules and ducts produces a more or less formless mass of cells. Close examination reveals an intact basement membrane, absence of mitosis and invasion, fatty degeneration of the epithelium and marked invasion of the gland by phagocytes.

While the ultimate decision rests on microscopic sections, the diagnosis can usually be made macroscopically. Cancer is never encapsulated but is usually circumscribed. It is firm to the touch, and when sections are cut there is noted the grittiness of an unripe pear. The cut surface is concave and white, with yellow streaks and areas of necrosis. From a comedo or duct cancer wormlike masses can be expressed. In fibro-adenoma the consistency varies from firm to soft. Section reveals that the tumor is encapsulated, and the cut surface usually corresponds more or less closely to the surrounding breast. If the normal proliferative and involutionary changes characteristic of this physiologic period are borne in mind, there should be little difficulty in distinguishing fibro-adenoma from cancer.

If an encapsulated tumor is larger than one quadrant of the breast, Bloodgood (1917-1929) recommended that it be regarded as a sarcoma and treated as such. Sarcoma of the breast, however, is not a common lesion. Fox (1934) noted only 60 sarcomas in a series of about 3,500 lesions of the breast. Of this number 22 arose in fibro-adenomas, being more frequent in the intracanalicular type. They occurred usually in fibro-adenomas of long standing, with the average age of onset between 45 to 50. Stout (1932), Semb (1930), McFarland (1926, 1927) and others have reported cases in which a sarcoma arose in a fibro-adenoma, and the report of 1 possible case of sarcoma is included here.

#### REPORT OF A CASE

CASE 14.—Mrs. M. M., aged 34, when five months pregnant, noted a lump in the left breast about the size of a 5 cent piece. The mass increased in size

until the onset of lactation and then ceased to grow. The breast lactated normally for nine months. When the patient was seen (Sept. 20, 1927), ten months after delivery, the tumor was 16 cm. in diameter and occupied practically all the breast. The superficial vessels were dilated, resembling varicose veins. There was no edema or pigskin, nor was the nipple retracted. The tumor was not adherent to the chest wall. Milk could be expressed from the nipple following manipulation of the tumor. The surrounding breast was lumpy. The axillary nodes were not palpable. Operation was performed on September 27.

As the appearance of the frozen section suggested a diagnosis of sarcoma, the breast and the underlying pectoral muscles were removed. The tumor was observed to be encapsulated, and on section milk could be expressed. The macroscopic impression was sarcoma or intracanalicular fibro-adenoma with lactation hypertrophy. Microscopically (fig. 9) the tumor was an intracanalicular fibro-adenoma that was partially hyalinized, with areas of lactation hypertrophy undergoing involution. The fibrous tissue response was extreme, and many mitotic figures were observed. Young connective tissue cells which did not invade the stroma or destroy the lobular structures surrounded the ducts and acini concentrically. The cells were concentrated next to the basement membrane of the ducts and acini, gradually diminishing in number as the distance from the parenchymatous structures increased to blend imperceptibly with the supporting framework.

This picture suggested a sarcoma confined within an encapsulated tumor, but the absence of any history of growth during lactation, the absence of invasion and destruction, the uniform arrangement of the connective tissue, the hyalinization of much of the tumor and the lack of metastasis were against a diagnosis of sarcoma. The fact that the patient is living and well eight years after operation is additional proof that the tumor was probably benign. This, however, is not infallible, because 13 (60 per cent) of the 22 patients with sarcoma arising in fibro-adenoma reported on by Fox were living and well from three to nineteen years after mastectomy, the average duration being eight years. Therefore, though this might be a case of a cured malignant sarcoma, the bulk of evidence points to its benignancy.

The differential diagnosis of sarcomas not arising in fibro-adenomas should offer no difficulty. The tumor may be of two types, fascial or neurogenic. Grossly, such lesions are not encapsulated, and the cut surface is homogeneous, soft and fleshy, with none of the necrotic areas or striations of cancer. Microscopically, whether fascial or neurogenic in type, they are composed of elongated spindle cells, with numerous mitotic figures and occasional tumor giant cells. The tumor rapidly invades and destroys the surrounding breast tissue.

Lactation mastitis, galactocoele, fat necrosis and tuberculosis also must be considered in making a diagnosis. Lactation mastitis usually occurs during the first three months of lactation. The lump is hot, tender and painful, and the overlying skin may be reddened. If resolution or abscess formation does not take place in two weeks, the mass should be explored. Microscopically the picture is one of inflammatory

change with destruction of the lobular structures. Galactoceles are commonly seen during lactation and usually follow lactation mastitis. Grossly, cystic spaces filled with milk are noted. Histologically they are observed to be composed of a fibrous wall infiltrated with inflammatory cells.

In fat necrosis a history of trauma is usually obtained. On section the lesion is observed to be circumscribed and usually small. It may be

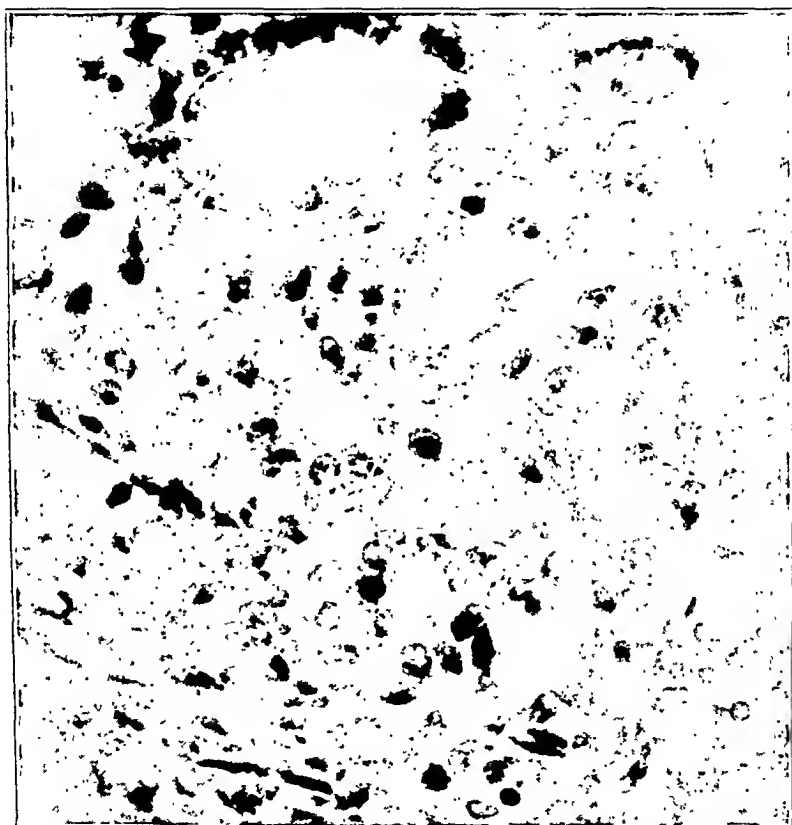


Fig. 9 (case 14).—Photomicrograph of a possible sarcoma arising in a lactating adenoma. The tumor had been present for fourteen months. It grew rapidly during pregnancy and failed to grow during lactation. The patient is living and well eight years after the operation.

cystic, with an oily or fatty content. There may be patchy areas of calcification. Microscopically the diagnosis is based on the amount of destruction of breast tissue and on the presence of calcified material, cholesterol crystals, giant cells and occasionally blood pigment. Evidence of tuberculosis, though uncommon, is usually found in patients with pulmonary tuberculosis. The presence of a sinus is pathognomonic of the

condition. Microscopically the typical picture includes caseation, giant cells, epithelial cells, lymphocytes and a fibrous tissue reaction.

Any lump in the breast noted during pregnancy or lactation should be explored immediately unless the patient is under 25 or unless the lesion resembles lactation mastitis. In the case of mastitis, two weeks may be allowed for involution or abscess formation. Since the diagnosis cannot usually be definitely established without making a frozen section, the patient should be prepared for a complete operation when removal of tissue for biopsy is undertaken. If the patient is lactating the breast should be emptied before exploration. After the tumor is exposed the presence of a capsule should be determined and a section taken. The wound should then be cauterized with 50 per cent zinc chloride, after the method of Bloodgood (1917, 1929). If the lump is benign, it should be excised with a margin of normal breast tissue. If the tumor is larger than one quadrant of the breast and is of the spindle cell type, it should be treated as a sarcoma, and the breast should be removed. After a biopsy the nursing of the infant is permitted.

It is preferable to remove these tumors during pregnancy, when the breast is less vascular and when there is less secretory activity than during lactation. If a lump which grows rapidly during pregnancy is left in the breast it may enlarge sufficiently to produce symptoms requiring surgical intervention when circumstances are such that complete removal of the breast may be necessary, whereas local excision earlier in pregnancy would have saved the breast. Lactation also increases the changes of postoperative complications, hematoma and mastitis. However, in the cases considered here no such complications occurred.

Nine of the patients in this series are living and well five years after operation, 6 are living and well after less than five years. Twelve patients have not been heard from lately but were living and well when last heard from. One patient died after five years, the cause of death being unknown. No interference with subsequent lactations or pregnancies was recorded.

#### SUMMARY

A report is made on 27 fibro-adenomas removed during pregnancy and lactation or present during that period and removed at varying intervals following the cessation of lactation. It was observed that the tumors were modified by pregnancy and lactation and that the changes produced in them were similar to those occurring simultaneously in the surrounding normal breast. The endocrine factors involved in the development and function of the breast are chiefly discussed, and it is suggested that the changes observed both in the breast and in the fibro-adenoma are of hormonal origin.

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## "OSTEOID-OSTEOMA"

A BENIGN OSTEOBLASTIC TUMOR COMPOSED OF OSTEOID AND  
ATYPICAL BONE

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The present article is a report on five cases of a type of benign neoplasm of bone apparently not hitherto classified. All the cases came to my attention during 1933.<sup>1</sup> They had the following features in common: 1. The patients were all adolescents or young adults from 11 to 22 years old. 2. In each case the principal complaint was of local pain, usually increasing and often severe enough to interfere with sleep. It was this symptom that brought the patients to consult a physician. 3. Uniformly, the lesion originated in an area of spongy bone. Although it sometimes involved cortical bone, it never penetrated the periosteum. 4. As observed roentgenographically, the pathologic areas were roundish, clearly circumscribed and confined within the bone. 5. The lesions were small and closely similar in size: Two were about 0.5 cm., two were 1 cm., and one was 2 cm., in diameter. 6. In every case operation was performed on the assumption that the condition was inflammatory—osteomyelitis or an abscess of the bone—but pus was not found in any instance. 7. Complete eradication resulted in the eventual disappearance of all symptoms without recurrence of the local condition.

*CASE 1.—History.*—The patient was a man 22 years old who first came for treatment to the outpatient department on June 14, 1933. Two years before admission to the hospital his left ankle began to be tender anteriorly. Stiffness in the region and limping developed, apparently in consequence of the pain. The pain gradually became worse and was believed to have been aggravated by some stretching treatments given by an osteopath about three months before the patient was seen at the clinic. The pain now radiated down the ankle anteriorly. The limp which was developing remained constant. The patient remembered that about four years before he slipped and injured the ankle. A hematoma formed anterior to the external malleolus. However, this resolved within a few days, and no symptoms referable to the ankle appeared until two years later. Neither at the time of admission nor previously was there difficulty in connection with any other joint region.

*Examination.*—Clinical examination revealed that a large area of the dorsal surface of the left foot (over the head of the astragalus and extending in front of the malleoli) was tensely swollen. There was no redness or local heat, however.

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1. Since this manuscript was submitted I have encountered three additional instances of the condition to be described. These cases coincide very closely, in regard to both clinical and pathologic manifestations, with the five cases to be discussed in the present article.



Forced dorsiflexion was somewhat restricted and painful, and there was marked tenderness on deep pressure on either side of the tibialis anticus tendon. The rest of the clinical examination and the clinical laboratory tests yielded nothing worthy of note.

A roentgenogram taken on June 16 revealed the presence of a circular abnormality in the superior portion of the neck of the astragalus (fig. 1). The pathologic area lay directly in front of the trochlea and measured roughly 1 cm. in diameter. As the roentgenogram demonstrated, the lesion created a bulge in the contour of the superior surface of the neck of the bone. It was apparent roentgenographically that near the periphery of the globuloid lesion there was an annular zone that was demarcated from the rest of the lesion by its lesser permeability to light. The hollow in the astragalus was likewise delimited by such a zone.



Fig. 1 (case 1).—Roentgenogram showing the circular lesion with its central core in the superior portion of the neck of the astragalus. The lesion was about 1 cm. in diameter.

Intermediary between the darker zones was a lighter one. The core of the lesion was also relatively highly permeable to light.

*Operation.*—An operation was done on June 29 on the assumption that the lesion in the astragalus was a sequestrum associated with osteomyelitis. At this time Dr. Sashin found the tissues overlying the upper surface of the astragalus very edematous and much thickened, while the neck of the bone was somewhat bulged out. A shell of surface was lifted with an osteotome. Underneath the shell a lump of bone was found which was easily lifted out. It corresponded in size and shape to the abnormal shadow observed in the roentgenogram.

*Bacteriologic Study.*—Culture of the material removed at operation revealed a diphtheroid bacillus. A guinea-pig inoculated with some of the material died

eighteen days later. At its autopsy considerable postmortem changes were found, but there was no evidence of tuberculosis either grossly or microscopically.

*Course.*—The postoperative course was satisfactory. Within four months after the operation the wound had completely healed and the patient was able to bear full weight on the foot. A control roentgenogram taken ten months after the operation revealed that the defect in the astragalus created by removal of the lesion had been filled in. The healing had proceeded to almost total replacement of the previously diseased area by healthy tissue.

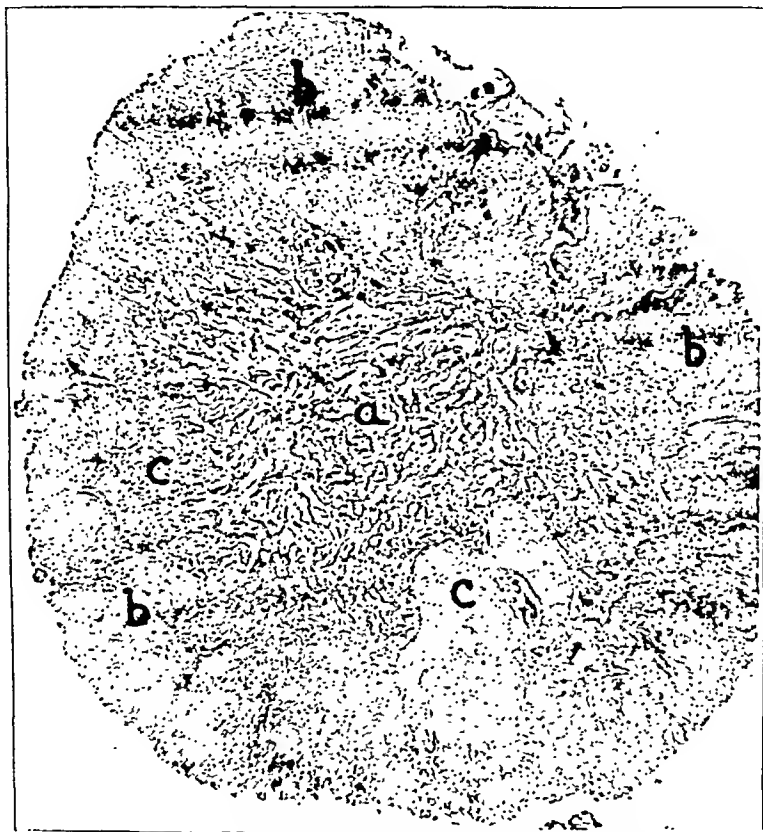


Fig. 2 (case 1).—Photomicrograph (magnification,  $\times 10$ ) of the lesion shown in figure 1. Note the core of newly formed trabeculae with cellular intertrabecular marrow (a), the peripheral zone of calcified osteoid (b), and the intermediary zone of uncalcified osteoid (c).

*Pathologic Observations.*—The so-called sequestrum from the left ankle was seen on gross inspection to be a mass of rather soft bony tissue. Serial paraffin sections revealed no trace of original bone. The tissue was composed essentially of (1) osteoid, large areas of which, especially in the periphery, were calcified, and (2) a network of very thin, newly formed, more or less centrally placed trabeculae between which there was (3) a loose, highly vascular fiber marrow (fig. 2).

The histogenesis of the lesion could be read microscopically. It was apparent that the formation of osteoid through the agency of osteoblasts constituted an important feature of the pathologic process. What was even more significant was the calcification of the osteoid, observed especially around the periphery of the lesion. The abundant formation of osteoid was not, of course, unaccompanied by osteoclasts, however. Everywhere in the sections, reconstruction, especially through resorption of the calcified osteoid, was in progress. Numerous osteoclasts were to be observed where the reconstruction was most active. It was near the sites of destruction and removal of the denser and calcified osteoid that the formation of new osteoid through the deposition of intercellular material between osteoblasts was most lively (fig. 3).



Fig. 3 (case 1).—Photomicrograph (magnification,  $\times 50$ ) showing histologic details at the periphery of the lesion. Note the calcifying osteoid (a), and the zone between the tumor (b) and the perifocal original bone (c).

As already noted, the more central portion of the lesion was occupied by a network of delicate trabeculae. These were covered by osteoblasts which seemed to be actively depositing new bone. Many of these trabeculae were indented by Howship's lacunae containing osteoclasts. Between these trabeculae was a loosely fibred, highly vascular osteogenic mesenchymal connective tissue.

Several additional fragments of bone were studied which had been curetted from the part of the astragalus cupping the total globuloid neoplastic mass of osteoid and new bone. These showed that the original bone trabeculae in these fragments had been thickened somewhat by the deposition of new lamellar bone.

Their architecture had also been somewhat modified by resorption. Between these thickened trabeculae of lamellar bone was a fatty fiber marrow. The globuloid neoplastic mass of osteoid and new bone was clearly differentiated but was not bound off from the sclerotic perifocal spongy bone by any special capsule or border.

*Interpretation of the Roentgen Findings.*—In the light of the pathologic observations one can see why the core of the lesion was relatively highly permeable to the roentgen rays (fig. 2). This core consisted of a delicate reticulum of poorly calcified new bone and osteoid. The relative darkness of the annular zone within the periphery of the lesion was due to the fact that the tissue in that zone consisted of densely compacted calcified osteoid. The hollow in the astragalus cast a denser shadow because it was composed of spongy trabeculae which had become some-



Fig. 4. (case 2).—Roentgenogram showing the dense, homogeneous, circular shadow in the sulcus of the calcaneus.

what sclerotic. The intermediate shadow of relatively high permeability to light was found to be due to the presence of osteoid that had not calcified.

*CASE 2.<sup>2</sup>—History.*—The patient was a girl 11 years old who was admitted to the University Hospitals, Iowa City, on April 21, 1933.

In the previous August the patient twisted her right foot. In spite of this she was able to play and walk, but two weeks later her ankle began to be painful. Toward the end of December 1932 the pain became worse, especially at night.

*Examination.*—Clinical examination revealed a swollen ankle which was very tender, especially on the inner side. Motion was markedly painful, and there was muscle spasm. The muscles of the thigh and calf showed atrophy. The clinical laboratory tests yielded negative results.

2. The data on this case were made available by Dr. Ernst Freund of the Department of Orthopedic Surgery, State University of Iowa, College of Medicine.

The roentgenogram, a print of which was also submitted by Dr. Freund, disclosed a lesion in the upper anterior portion of the calcaneus in the region of the sulcus (fig. 4) which showed as a dark (i. e., relatively less light-permeable) disk about 6 mm. in diameter, surrounded by a narrow, faint, lighter ring. Much other bone of the calcaneus in the vicinity of this circular lesion was also less permeable to light than more remote portions of the bone, apparently because of perilesional osteosclerosis.

*Operation and Course.*—Exploration of the subastragaloid region was performed on May 1. The specimen to be described later was removed at this time.

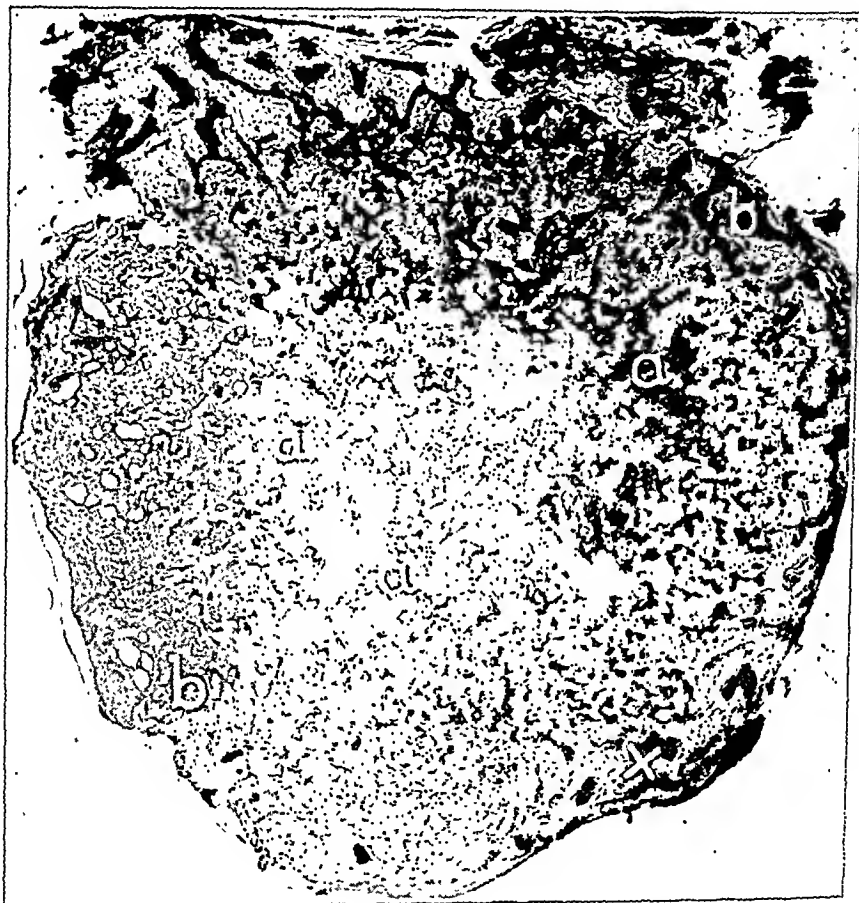


Fig. 5 (case 2).—Photomicrograph (magnification,  $\times 15$ ) of the lesion shown in figure 4. Note the osteoid tissue (*a*), which is heavily calcified in some places, the peripheral trabeculae of new bone (*b*) and the peripheral region (*x*).

The postoperative course was uneventful. Six months after the operation the patient still had some pain in the foot but much less than before. Five months after the operation she had acute tonsillitis, during which there was intense pain in the foot.

*Pathologic Observations.*—The general histologic appearance of the lesion was striking and characteristic (fig. 5). The circular, rather sharply delimited lesion, which appeared in the roentgenogram to be about 6 mm. in diameter, consisted almost entirely of densely compacted osteoid, much of which was in process of calcification. At the extreme periphery of the lesion a thin zone of trabeculae

was present. Between these trabeculae was loose vascular fatty and fiber marrow containing numerous blood vessels. The layer of trabeculae was encircled in turn by a thin layer of encapsulating connective tissue. The resemblance of the lesion to that found in case 1 was apparent even at first glance.

What was striking and characteristic in the lesion was the osteoid structure. The section was stained with hematoxylin and eosin. Large quantities of intercellular material staining pink were observable everywhere. This material crowded and compressed the cells. It was also apparent, however, that scattered through the osteoid mass were innumerable tiny areas in which the osteoid was in the process of being calcified and converted into a primitive type of bone (fig. 6). In the area where the conversion was taking place the vascular spaces had become

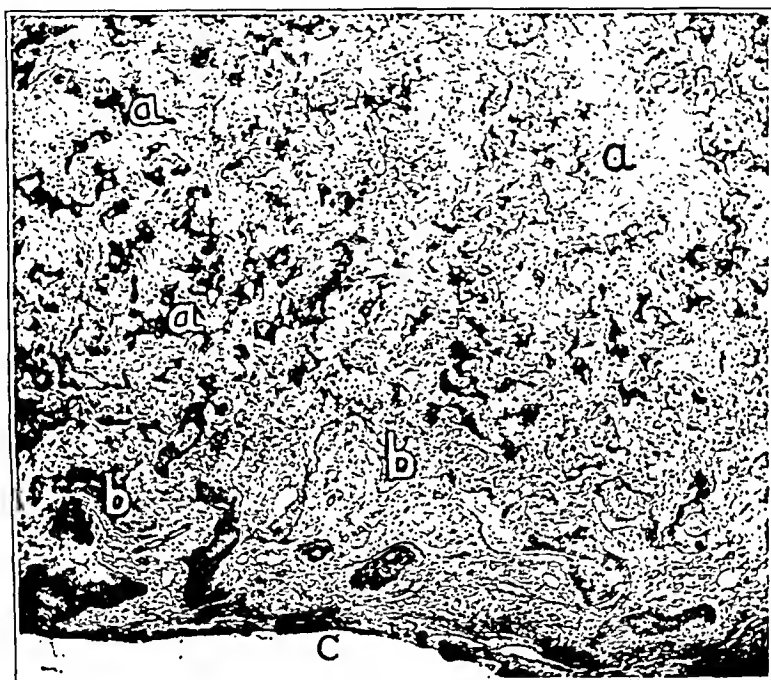


Fig. 6 (case 2).—Photomicrograph (magnification,  $\times 50$ ) of the peripheral region (x) in figure 5. Note the osteoid that is calcifying (a), the peripheral trabeculae of new bone which become continuous with the osteoid (b) and the periphery of the lesion (c).

more clearly delimited. Furthermore, the primitive bone already showed evidences of reconstruction, denoted by the presence of Howship's lacunae and osteoclasts. The few better developed bone trabeculae at the extreme periphery of the lesion were apparently evidences of further progress of ossification.

*Interpretation of the Roentgen Findings.*—In the light of the histologic examination it was apparent that the reason the mass of the lesion was relatively not very permeable to light was that it was composed of osteoid which in innumerable places was being calcified and converted into atypical primitive bone. The reason the perifocal bone was also relatively only slightly permeable to light was that the original trabeculae of the calcaneus had become sclerotic.

CASE 3.—*History*.—The patient was a white girl 20 years old who entered the outpatient department on Nov. 22, 1933.

For about a year the patient had pain in the middle toe of the right foot. The pain was most troublesome at night, especially when she assumed a recumbent



Fig. 7 (case 3).—Roentgenogram showing the dense, homogeneous, circular shadow in the ungual phalanx. The bone has expanded. The proximal portion of the phalanx is sclerotic.

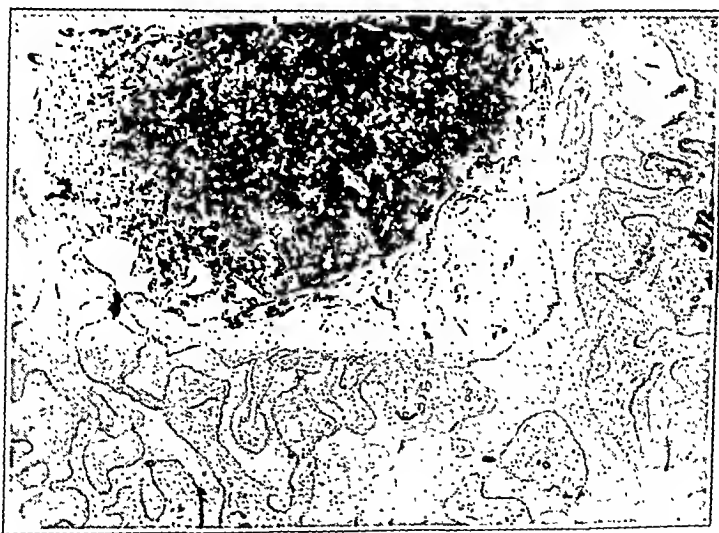


Fig. 8 (case 3).—Photomicrograph (magnification,  $\times 15$ ) of part of the focus shown in figure 7. It is composed of highly calcified, atypical bone which stands out clearly from the sclerosed perifocal bone.

position. Recently it had become so severe that sometimes she could not sleep. The pain was localized, nonradiating, constant, dull and aching. There was no history of injury or of fever or chills.

*Examination.*—Clinical examination revealed moderate swelling of the terminal end of the toe. The swollen tissues were firm. There was no fluctuation. The ungual end of the toe was tender, and the nail was discolored. The swelling and discoloration were apparently of recent date as compared with the duration of the pain. The results of the clinical laboratory tests were negative.

A roentgenogram taken on November 25 showed in the terminal end of the ungual phalanx a circular lesion 5 mm. in diameter (fig. 7). The pathologic area cast a dense and relatively homogeneous shadow. It was delimited from the rest of the phalanx by an annular zone comparatively permeable to light. Just proximal to the lesion the bone appeared somewhat densified. Before pathologic examination the lesion was erroneously interpreted as a sequestrum.

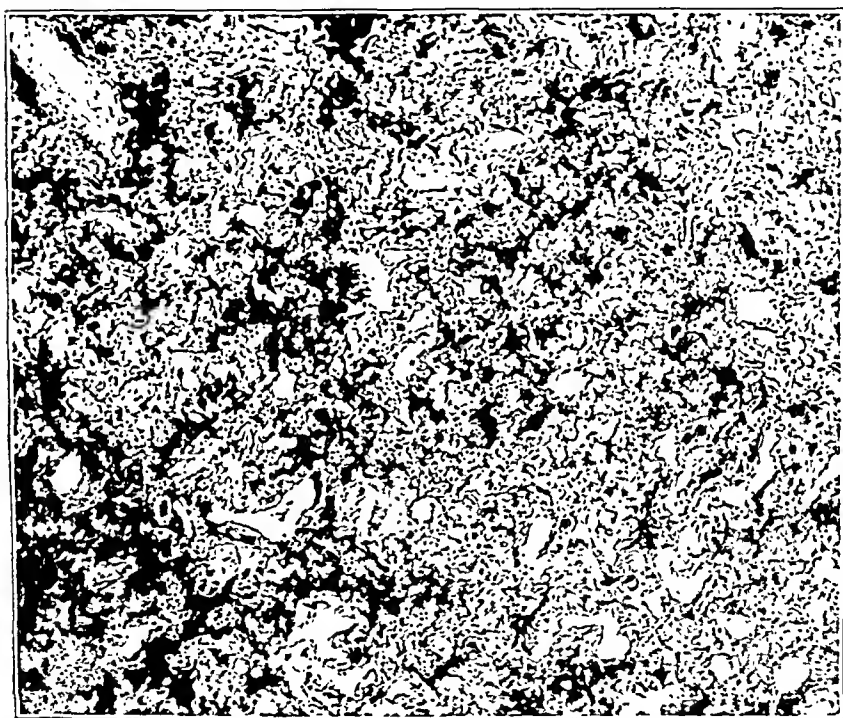


Fig. 9 (case 3).—Photomicrograph (magnification,  $\times 125$ ) showing details of the histologic structure of the atypical bone constituting the focus shown in figure 8.

*Operation and Course.*—An operation was performed on December 4 by Dr. Milch on the assumption that the condition was osteomyelitis of the right middle toe with formation of a sequestrum.<sup>3</sup> The diseased portion of the phalanx was resected.

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3. After the pathologic examination of this specimen had been made, but before I had completed my study of this and similar cases, Dr. Milch published a report (J. Bone & Joint Surg. 16:681, 1934) in which some of the data (largely clinical) concerning this case were included. He also mentioned some facts concerning cases 1 and 5 of the present series.



The postoperative course was smooth so far as primary healing and freedom from intercurrent infection were concerned. Six months after the operation, however, there was still swelling of the soft tissues of the ungual portion of the toe. Also, the tissue about the nail was still tender on pressure. The lesion has not recurred, however.

*Pathologic Observations.*—On gross examination the resected fragment of the phalanx showed a yellowish focus of changed bone. Microscopically this focus was found to be definitely circumscribed and to consist of a highly compact mesh of rather atypical and primitive bone (fig. 8). The primitiveness of the bone was evidenced in the multiplicity of the bone cells, the prominence of the bone cell lacunae and the irregularity of the arrangement of the cells. Between the meshes of bone were numerous vascular channels. These meshes were lined by osteoblasts, and reconstruction was evidenced by the presence of Howship's lacunae and osteoclasts. No hematopoietic marrow was present between the trabeculae.

The possibility was considered that the substratum of this focus of primitive bone might possibly be cartilage which had undergone direct bony metaplasia. Careful search of serial sections failed to disclose any cartilage, however. Furthermore, the cellularity of the lesion strongly indicated that such cartilage could scarcely have constituted the direct precursor of this tissue. (The primitive bone observed in this lesion reminded me of the sclerotic atypical bone seen in the metaphyses of rats which were on a diet adequate in calcium but which were suffering from chronic hyperparathyroidism.) All in all, the impression gained was that the lesion in its present state was the product of rapid ossification of the osteoid tissue, with the production of primitive bone (fig. 9). The ossification of the osteoid tissue observed in case 2 seems to shed light on the genesis of the primitive bone in the present lesion.

The perifocal original bone showed thickening of the spongy trabeculae through apposition of new bone. The intertrabecular marrow was moderately scarred, and fatty fiber marrow had appeared. The neoplastic focus, although delimited from the surrounding sclerotic bone, was again not walled off from it in any special way.

*Interpretation of the Roentgen Findings.*—The pathologic observations made it clear that the reason the circular lesion in the terminal end of the ungual phalanx cast a homogeneous dense shadow was that it was composed of a mesh of highly compact and highly calcified bone which histologically was primitive (fig. 9). There was no evidence either of osteomyelitis or of formation of a sequestrum.

*CASE 4.—History.*—The patient was a youth 16 years of age who first came to the outpatient department for treatment on Oct. 21, 1933. Four months before this the patient began to have pain in the back of the neck which was dull and nonradiating.

*Examination.*—On clinical examination it was striking that no anterior flexion of the head could be elicited beyond the neutral plane. In most other directions there was some motility, especially toward the right. The cervical portion of the spine was tender both to touch and to pressure, particularly in the region of the spinous process of the seventh vertebra. However, there was no local heat or redness, and no masses could be felt. In the course of four months of observation in the clinic the cardinal symptoms progressed; that is, the pain and inability to bend the head forward became more pronounced. Pain continued despite immobilization of the neck in a leather jacket and often interfered with the patient's sleep.



Fig. 10 (case 4).—Roentgenogram showing the circular area of rarefaction in the expanded spinous process.



Fig. 11 (case 4).—Photomicrograph (magnification,  $\times 10$ ) of the lesion in the spinous process shown in figure 10. Note how clearly the pathologic tissue stands out from the surrounding bone.

Roentgen examination at the time of the patient's admission to the outpatient department failed to disclose any lesion in the cervical portion of the spinal column. Four months later, however, examination of this region disclosed a circular area of rarefaction in the spinous process of the last cervical vertebra. The diseased area (fig. 10) measured about 20 mm. in diameter. About the lesion the bone of the spinous process appeared somewhat sclerosed, while that of the body of the vertebra was sclerotic to a considerable degree.

*Operation and Course.*—An operation was performed by Dr. Wishner on Feb. 26, 1934, on the assumption that the condition was osteomyelitis of the spinous process of the last cervical vertebra. This process was removed.

The postoperative course was one of slow improvement with respect to the principal complaints. Nine months after the operation flexion of the head beyond the neutral position was impossible. Hyperextension was normal, however, and the pain had considerably diminished.

*Pathologic Observations.*—On gross examination the spinous process was found ballooned out. In the expanded portion the cortex had thinned, at least in one place, to the point of incipient perforation. In the medullary space was a circumscribed lesion containing bone different from that surrounding it (fig. 11). On microscopic examination the tissue in the medullary space was found to be composed of a fine-meshed, compact network of osteoid and bone. In places the osteoid was in a process of calcification. This reticulum of osteoid and new bone was everywhere lined by osteoblasts. In Howship's lacunae on the surface of the trabeculae and between the trabeculae themselves osteoclasts were seen. The intertrabecular marrow was vascular, and the vessels were engorged. This marrow contained large numbers of osteoblasts. The lesion was definitely delimited from the original bone of the spinous process but there was no special delimiting tissue. The focus was surrounded by a zone of vascular connective tissue which was continuous with the intertrabecular marrow of the adjacent bone. This bone showed considerable resorption and numerous osteoclasts in the immediate vicinity of the intra-osseous lesion. Farther off there was definite evidence of sclerosis. In some spots actual thickening of the cortex of the spinous process through deposition of periosteal new bone had occurred.

*Interpretation of Roentgen Findings.*—This was the only case in which I was fortunate enough to have roentgenograms of the diseased region taken both before and after the pathologic condition was demonstrable in this way. The first roentgenogram failed to disclose the disease focus, although the clinical complaints were already clear. Roentgen examination four months afterward, however, disclosed the area of rarefaction already described. In the interim the clinical complaint had become aggravated. The difference between the two roentgenograms was evidence that the lesion had progressed. The reason the lesion showed as an area of rarefaction was that the osteoid was not highly calcified as it was in cases 2 and 3. In fact, on gross examination the intramedullary mass felt like an accumulation of granulation tissue.

*CASE 5.—History.*—The patient was a white youth 15 years of age who first came for treatment to the outpatient department on May 1, 1933.

The complaint was of pain in the ankle of two months' duration and of increasing severity. The pain was generally nocturnal and was sometimes severe enough to prevent sleep. It did not radiate. There was no recollection of any injury.

*Examination.*—Clinical examination revealed puffiness of the left ankle with tenderness above the external malleolus. There was distinct limitation of function in that the patient favored his left foot. The swelling was mainly in the vicinity of the external malleolus. There was slight local heat but no fluctuation or redness. Marked point tenderness was noted over the fibula about 2 inches (5 cm.) proximal to the tip of the malleolus. The clinical laboratory examinations yielded negative results.

Roentgen study revealed a roundish area relatively more permeable to light, about 1 cm. in its greatest diameter, in the medulla of the fibula. The lesion appeared as a sort of vacuole and was located approximately 1 inch (2.5 cm.)



Fig. 12 (case 5).—Roentgenogram showing the area more permeable to light in the lower end of the tibia. There have been some expansion of this bone and some deposition of periosteal new bone.

above the epiphyseal line (fig. 12). The area stood out sharply from the neighboring bone. The surrounding medullary bone was somewhat sclerosed. The distal end of the fibula was thickened in consequence of periosteal depositions.

*Operation and Course.*—An operation was performed on May 11 on the assumption that the condition was an abscess of the bone. However, no pus was found in the region explored, and pieces of tissue sent to the laboratory for culture remained sterile. The patient was discharged on June 6 but was readmitted to the hospital on June 19 because the operation had not relieved the pain, which, in fact, had become worse. Furthermore, a new roentgenogram showed that the lesion revealed in the earlier roentgenogram, had not been removed. A second

operation was performed by Dr. Reitzfeld on June 22, still on the assumption that the lesion was an abscess of the bone, but no pus was found in the diseased area, which was curetted.

*Pathologic Observations.*—Since the material submitted consisted only of small curetted fragments, no diagnostic opinion was expressed on the basis of the gross findings. Microscopic study revealed an osteoblastic, osteoid and bone-forming lesion (fig. 13). Collections of osteoblasts were observed, between which intercellular material had become deposited so that small osteoid masses were formed. In places, the osteoid showed some evidence of calcification. Both the calcifying and the uncalcified osteoid collections were definitely undergoing resorption, and

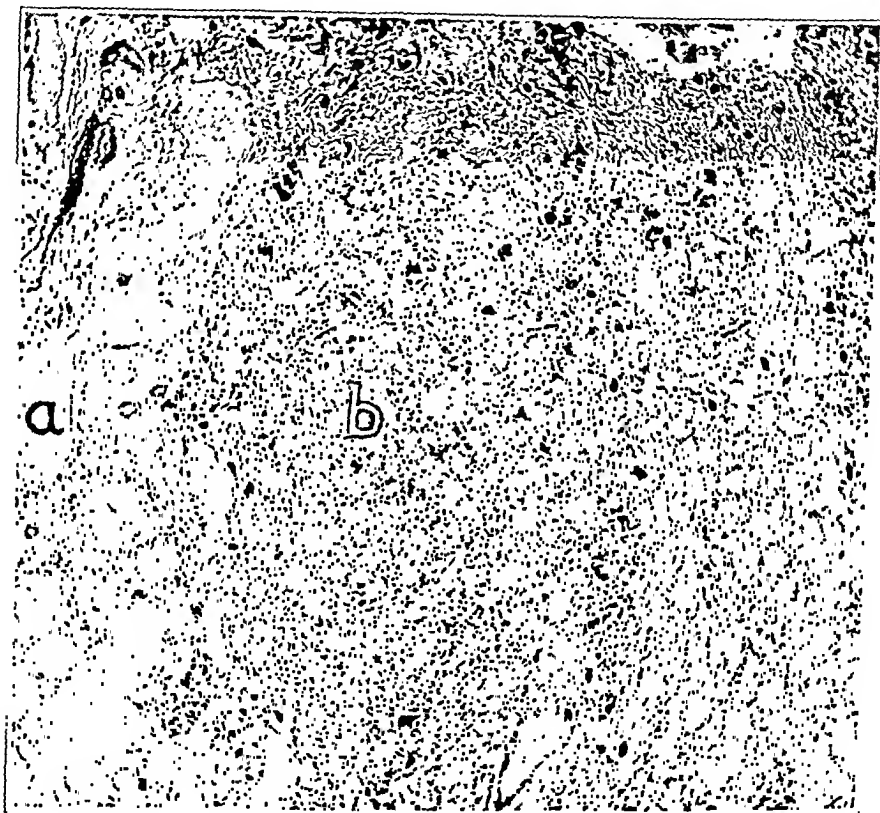


Fig. 13 (case 5).—Photomicrograph (magnification,  $\times 65$ ) of tissue curetted from the area of disease shown in figure 12. Note the original bone trabeculae (a) and cellular pathologic tissue (b) containing numerous osteoclasts and osteoid trabeculae, a few of which show evidences of calcification.

numerous osteoclasts were observed near and between them. The intertrabecular tissue was composed of spindle and reticular elements clearly capable of forming osteoid and bone. There was no special border zone delimiting the lesion from the neighboring original bone of the fibula, the encompassing trabeculae of which were slightly sclerosed. The osteoid aggregations in this lesion showed less calcification than did those in the cases previously described.

*Interpretation of the Roentgen Manifestations.*—As previously noted, the lesion appeared merely as a roundish area in the bone relatively more permeable to light

than the surrounding bone. This was due to the fact that the lesion was composed essentially of masses of osteoid that had not yet become calcified. It is not until calcification occurs that annular dense shadows like those observed in cases 2 and 3 are to be observed.

#### COMMENT

*Possible Inflammatory Origin of the Lesion.*—It was clear from the pathologic anatomy that the condition was in no sense the result of inflammation—suppurative or granulomatous. In the first place, there were no microscopic indications of suppuration or suppurative liquefaction such as would point to pyogenic inflammation. Again, no specific or nonspecific granulation tissue was evident such as one would expect to find if the condition had arisen through inflammation. Also, no necrotic bone was revealed in any of the specimens, although one expects to find it in osseous inflammations even if clearly defined sequestrums do not appear.

The microscopic observations did not even support the assumption that an inflammation had been present, had subsided and had been healed through the formation of new bone (sclerosing osteomyelitis). If the present condition had so arisen, residua of inflammation would still be discernible since all the lesions were in the formative stage when seen. Finally, the whole general character of the microscopic pathologic observations tends to exclude the possibility that the lesions had developed from a healing inflammatory process.

*Possible Origin from an Embryonic Rest.*—The supposition that the lesions might be rests, either static or growing, can likewise be controverted. It is known that simple rests in bone do not give rise to clinical symptoms. Also, cartilaginous rests are the sort most likely to be found within a bone, and no traces of cartilage were discovered in the lesions reported on here. Furthermore, although cartilaginous rests are known to undergo bony transformation at times, resulting in enostoses, there are no clinical symptoms connected with their transformation into bone. Enostoses of this type are encountered only accidentally, either by the roentgenologist or by the pathologist. They are most likely to be found in the spongy portion of long tubular bones. They consist of normal adult lamellar bone but are distinguished from the neighboring normal spongy bone by their denser, pumice-like consistency. The character of such enostotic bone differs in every way from that of the tissue of the lesions reported on here.

*Lesions as Unfamiliar Healing Stages of Giant Cell Tumors or of Cysts.*—Pathologic examination revealed that the lesions under discussion could not be explained as the healing stage of these conditions. In the first place, if the lesions were healing giant cell tumors it was to be expected that they would still show microscopically the distinctive characteristics of such tumors, that is, a highly vascular spindle stroma,

often with an abundance of multinucleated giant cells. Furthermore, while formation of bone is not infrequently to be observed in giant cell tumors, it is never excessive nor is the appearance of bone preceded by a stage of exuberant formation of osteoid.

It would not be appropriate here to consider the relation of giant cell tumors of bone and local osteitis fibrosa to certain cysts. There are several different ways in which a circumscribed cyst of bone may arise. In any event, cystic cavities in bone are usually lined by a definite fibrous membrane. Also, the natural tendency for cysts to become obliterated through healing is slight. Intracystic ossification is not likely to occur. If a cyst is obliterated the bone pushes inward from around it, constantly reducing it. In the lesion under consideration there was no wall clearly delimiting the diseased tissue from the surrounding bone, and the core of the lesion was usually calcified osteoid or bone. It seems clear that this type of lesion cannot be regarded as a healed or healing cyst of the bone.

*The Neoplastic Nature of the Lesion.*—One feels forced to conclude that one is dealing here with a benign bone neoplasm the distinctiveness of which has not hitherto been recognized and which I am designating "osteoid-osteoma." The osteoid-osteomas so far observed have all arisen intramedullarily, in spongy bone areas. None have arisen from the periosteum or within cortical bone. I hold that this tumor arises from osteoblastic (bone-forming) mesenchyme; that it is peculiar histologically in its tendency to form rather large amounts of osteoid; that this osteoid can become considerably calcified; that new bone, largely atypical, may replace or intermingle with the osteoid, and, finally, that when trabeculae do form, the intertrabecular stroma remains highly cellular, containing numerous osteoblasts but never hematopoietic marrow or simple fatty marrow.

Roentgenographically each of the five tumors cast a small and annular shadow. In case 5 the shadow of the lesion was more permeable to light than the neighboring bone. In this case the tumor was composed essentially of uncalcified osteoid which had replaced the spongy trabeculae that would normally be present in this portion of the fibula. In my opinion this roentgenogram portrays one of the earliest visible manifestations of the lesion. The rarefaction shown in the roentgenogram signifies that the bone originally present at the site of the disease focus has been resorbed and has been replaced by osteoid. This process may be well begun, however, before it shows roentgenographically. This opinion was confirmed in case 4, in which there was considerable pain in the neck and inability to bend the head forward for several months before the spinous process showed the rarefaction induced by the tumor. When calcification and ossification have begun,

however, the roentgenogram of the lesion may show a shadow considerably darker than that of the surrounding bone; this was seen particularly in cases 2 and 3.

Among other reasons why it seems safe to regard the lesion as a neoplastic tumorous growth are the following: 1. The lesion consists of osteoid and atypical bone which without obvious cause has displaced the bone that would normally occupy the region. 2. The growth of the lesion, though slow, was independent of that of the surrounding tissues, the perifocal bone responding merely by becoming sclerosed. 3. Microscopically the tissue of the lesion differs from that of the surrounding normal bone but is itself homogeneous and consistently the same in the different cases.

As to the benignity of the tumor, this too is directly evidenced in several ways. The tumor does not perforate the periosteum or infiltrate the soft tissues in the vicinity of the bone. Also, in all these cases it was surrounded by encapsulating bone. Above all, after it had been removed it did not recur, and there were no metastases.

#### LITERATURE

Search of such literature as seemed reasonably promising (including roentgenologic atlases) did not reveal any full and consistent discussion or description of the type of lesion forming the subject of the present article. Under the title "Sclerosing Osteomyelitis of Carpal Scaphoid" Dr. Hitzrot<sup>4</sup> presented before the New York Surgical Society on Dec. 11, 1929, a case in which the roentgenogram closely resembles those made in my first three cases. The pathologic description was extremely cursory, however, and no details were given by which the lesion might be distinguished in similar cases. As judged, however, by the annular shadow in the roentgenogram, by the history of persistent, nonradiating pain and swelling and by the fact of non-recurrence, Hitzrot's case seems clearly to belong to the group under discussion.

There are two other reports to be considered as probably bearing on the type of lesion with which this article is concerned.<sup>5</sup> The first is

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4. Hitzrot, J. M.: Sclerosing Osteomyelitis of Carpal Scaphoid, *Ann. Surg.* **91**:450, 1930.

5. In addition, I have now come across a pertinent article by J. Heine (*Arch. f. klin. Chir.* **146**:737, 1927). In this article he described what he regards as a bone sequestrum in the process of being reincorporated into the basal phalanx of the ring finger. The roentgenogram of this so-called sequestrum certainly resembles very closely the roentgenograms of my cases 2 and 3. The pathologic evidence which he presented does not clearly support his contention that the lesion he was discussing was an inflammatory one.



that of Bergstrand,<sup>6</sup> who in 1930 reported two cases of what he considered "a peculiar and probably not hitherto described osteoblastic disease in the long bones of the hand and foot." One of his patients was a girl about 16 years of age with swelling and tenderness of the right foot of fifteen months' duration at the time of operation. A lesion of the metatarsal bone was known to have been in existence for at least thirteen months when operated on, and although the lesion did not enlarge during this time, it had become more painful since first noted. On roentgen examination the bone was found to have undergone spindle swelling. There was periosteal new bone formation; the underlying cortex was retained, and the marrow canal was partially obliterated. The entire diaphysis of the metatarsal bone was resected, and the patient made a complete recovery. The second patient was a boy 18 years of age. For two years there had been increasing thickness of the left middle finger. Roentgenologic examination revealed a destructive lesion in the distal half of the diaphysis of the basal phalanx. The phalanx was removed, and there was no recurrence during the succeeding three years. Pathologic examination in the two cases revealed eccentrically located disease foci situated, respectively, in the proximal portion of the diaphysis of the metatarsal bone and in the distal portion of the diaphysis of the phalanx. The disease focus, which in each case was the size of a pea, showed a center which consisted of amorphous collagenous material.

Bergstrand was at a loss to classify this condition. He held that it was neither a tumor nor an inflammatory process. He conceived the lesions as having arisen through a local disturbance in the formation of bone, tracing this disturbance back to embryonal life. Although no cartilage cells were observed on pathologic examination, he believed that the homogeneous intercellular material most closely resembled the intercellular material of cartilage, and that it had resulted from embryonal cartilage that had undergone regressive change leading to loss of its cells. He was of the opinion that the lesions would have healed spontaneously and the center of the focus would have been transformed into bone had they not been operated on.

Mayer and I<sup>7</sup> described an "osteoblastic osteoid tissue-forming" lesion of the metacarpal bone which, especially microscopically, showed a strong basic similarity to the lesion described by Bergstrand. The latter exchanged slides with me and like myself was definitely of the opinion that essentially we were dealing with the same condition. How-

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6. Bergstrand, H.: Ueber eine eigenartige, wahrscheinlich bisher nicht beschriebene osteoblastische Krankheit in den langen Knochen der Hand und des Fusses. *Acta radiol.* **11**:597, 1930.

7. Jaffe, H. L., and Mayer, L.: An Osteoblastic Osteoid Tissue-Forming Tumor of a Metacarpal Bone, *Arch. Surg.* **24**:550 (April) 1932.

ever, the lesion described by Mayer and me had progressed to a stage at which its tumorous character could no longer be questioned even clinically. The lesions in Bergstrand's cases, on the other hand, were still so circumscribed that he rejected the idea of their being tumors. In my opinion, however, they were tumors not only resembling the metacarpal tumor described by Mayer and myself but also possibly related to the lesions of the five cases described in the present article.

The "osteoblastic osteoid tissue-forming" metacarpal tumor seen and described by Mayer and me began when the patient, a girl, was 12 years old. At first it grew slowly. A biopsy was performed shortly after the tumor was first noticed by the patient. Microscopic examination revealed a richly cellular osteoblastic tissue which in places contained large deposits of intercellular material. The osteoid nature of the tissue at the sites of such deposits was clear. Growth of the lesion continued to be slow for the next two years, when growth suddenly became very rapid, destroying the entire metacarpal bone. After it had grown rapidly for about six months the tumorous tissue was extirpated. An encapsulated mass measuring 10 by 6.5 by 6 cm. was removed. In spite of the size of the lesion there had been no penetration of the periosteum. A conspicuous and peculiar microscopic feature of the tumor was the presence of considerable amounts of osteoid tissue, much of which showed no trace of calcification. There was complete absence of cartilage, cartilaginous elements and tumor giant cells. There has been no recurrence five years after resection of the tumor.

It must be conceded that there are conspicuous discrepancies between this metacarpal tumor and the present group of five lesions. Despite these differences, however, microscopically the tissue of the metacarpal tumor continued to resemble in a general way (as it did in the biopsy specimen) the pathologic tissue both in Bergstrand's cases and in the five smaller lesions herein described. It is this resemblance (along with the absence of recurrence up to five years after resection of the tumor) that makes me believe that the metacarpal tumor described by Mayer and myself was of the same nature as the lesions in Bergstrand's cases, in spite of the fact that he does not regard those in his cases as tumors. Furthermore, the osteoid character of the metacarpal tumor confirmed the suspicion that despite the special clinical symptoms which it created this tumor is related to the smaller and less exuberant lesions described in the present article. It is quite conceivable that some of the smaller lesions, if left to themselves, might ultimately also have come to show the sudden florid growth so striking in the metacarpal tumor and, vice versa, that at an earlier stage this tumor may have been small and circumscribed like the others.

#### SUMMARY AND CONCLUSIONS

Clinical, roentgenologic and pathologic details concerning five cases of a peculiar bone neoplasm have been presented. Analysis of these cases has led me to denote this lesion osteoid-osteoma and to single

it out in this way as a distinctive, not hitherto classified, type of bone neoplasm. It is a benign osteoblastic tumor composed of osteoid and atypical bone. In the cases seen it always arose intramedullarily in spongy bone areas.

All the patients were either adolescents or young adults. In every case the principal complaint was of local pain. As observed by roentgenogram, the pathologic areas were roundish and rather small. Complete eradication resulted in the eventual disappearance of all symptoms.

It has been shown that the lesion had no features suggesting an inflammatory origin or origin from an embryonic rest or that it represented an unfamiliar healing stage of a giant cell tumor, localized osteitis fibrosa or cyst. Despite the fact that the lesion of osteoid-osteoma remained small and globuloid in these five cases, the character of the pathologic tissue in the more diffuse tumor previously described by Mayer and me suggests that the latter lesion may be related to the type of tumor under discussion. Furthermore, it also seems likely that the lesion which was described by Bergstrand as being of embryonic origin and which he regarded as neither an inflammatory process nor a tumor is likewise related to the lesion herein designated as osteoid-osteoma.

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#### CORRECTION

In the article by Dr. Eldridge H. Campbell Jr., entitled, "Acute Abdominal Pain in Sickle Cell Anemia," in the October issue (*ARCH. SURG.* **31**:607, 1935), "better risk" in the penultimate line on page 619 should read "greater risk."

# MILD ACUTE APPENDICITIS

## APPENDICAL OBSTRUCTION

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The question as to what chronic appendicitis is and whether it ever exists has long since become trite. That there is a clinical entity consisting of a chronic disorder of the appendix is believed by most surgeons. Many appendixes continue to be removed because of so-called "chronic appendicitis." If there were no virtue in this practice one would expect it to present indications of ceasing to be the vogue. Statistics compiled from studies of the after-histories of patients whose appendixes have been removed because the organs seemed to be chronic disturbers of the peace lead to various conclusions. Enough favorable reports<sup>1</sup> have been given and sufficient observations have been made in their own practices to encourage the majority of surgeons to continue to remove appendixes because of chronic complaints. This is in spite of the fact that surgeons<sup>2</sup> as well as pathologists freely admit that definite chronic inflammation of the appendix is uncommon.

In order to understand better why there may be benefit from removal of appendixes showing little evidence of inflammation I have compared the complaints of a group of patients with the findings at operation and the condition of the appendixes removed. The series of appendixes studied consists of 344 removed in the past few years in one hospital. This series represents cases of frankly acute inflammation of the appendix and a number of cases in which the appendix was removed as a routine at operation on some other organ as well as cases of so-called chronic appendicitis. The last cases will hereafter be referred to as the chronic group. The observations made in the study of each of the different classes of cases will be recorded separately and afterward briefly correlated. The series of appendixes removed as a secondary consideration at the time of other operations has been used as a control group and will be referred to by that designation.

## CHRONIC APPENDICITIS

The indications<sup>3</sup> which have been put forth as evidences of the presence of chronic inflammation of the appendix are numerous. The

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From the Department of Pathology, College of Medical Evangelists.

1. Block, F. B.: Chronic Appendicitis: A Study of End Results, *M. J. & Rec.* **134**:448 (Nov. 4) 1931.

2. Dickson, W. M.: Chronic Appendicitis, *Brit. M. J.* **1**:184 (Feb. 3) 1934.

3. Letulle, M.: Surprises de l'appendicite chronique, *Presse méd.* **35**:1521 (Dec. 14) 1927.

situation is reminiscent of that of certain diseases for which no specific treatment has been found. The abundance of suggested signs of chronic appendicitis indicates that none of them is outstanding in cases ordinarily studied. If true chronic inflammation of the appendix exists the evidences of the activity must customarily be slight or they would be more easily recognized. Accordingly the series of chronic cases studied was expected to show little or no evidence of actual inflammatory phenomena.

Among the 344 cases studied there were 103 in which the appendix appeared to be the seat of trouble but in which it presented slight or no evidence of active inflammation. On examination it was found that many of the appendixes presented increased quantities of scar tissue in various layers, particularly, the submucosa. Some presented complete obliteration of their lumens. The scarring may be taken as evidence of previous inflammation, but is not to be regarded as an indication that inflammation was active when the appendix was removed. The presence of a few lymphocytes about the blood vessels in the outer layers might be taken as an indication of mild chronic irritation. This finding was observed rather frequently. Atrophy of lymphoid tissue was noticed many times.

The most constant and therefore most impressive evidences of abnormality in the 103 appendixes were indications of disturbed function rather than of inflammation. The name "appendicosis"<sup>4</sup> has been suggested for noninflammatory conditions in the appendix which are accompanied by clinical signs of what is commonly called "chronic appendicitis."

Before the appearances of the appendixes in the chronic group are discussed further a few clinical observations may be given. These will serve to accentuate somewhat the fact that the conditions treated were functional rather than inflammatory.

The almost universal complaint of the patients given a diagnosis of chronic appendicitis was of pain and more or less tenderness in the region of the appendix. The pain was more diffuse in some cases, and in a few, localized in the upper part of the abdomen. The pain was associated with nausea in 52 of the 103 patients; 22 had vomited at times. Pain, nausea and vomiting in most cases came in attacks lasting a few days at intervals of weeks or months. In some cases the complaints were almost continuous. Previous attacks were recorded in the histories of 95 of the patients. The average number of attacks was 5. The period during which attacks had been occurring varied from 2 weeks to 25 years, the average being 3.5 years.

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4. Steinberg, B.: Degenerative Lesions of the Appendix (Appendicosis) Hitherto Undifferentiated from Appendicitis, *Am. J. Clin. Path.* 1:339 (July) 1931.

The average temperature recorded as the patients entered the hospital was 98.6 F. The white blood cell counts taken just before operation varied from 3,600 to 13,500. The average count was 7,960 with an average neutrophil percentage of 59.7.

Nearly twice as many females as males were included in the group, there being 67 of the former and 36 of the latter. The age of the males varied from 13 to 62 with an average age of 32.8 years. Twenty of the 36 males were between 20 and 35 years of age.

The females varied in age from 9 to 54 years with an average age of 25, which is appreciably less than the average age of the males in this group. Thirty-four of the 67 females were between 19 and 29 years of age.

Twenty-nine of the 103 patients were having active attacks of pain with more or less vomiting and nausea at the time they were brought to the hospital for operation. The average duration of these attacks before operation was 3 days. The leukocyte counts taken just before

TABLE 1.—*Compression of Mucosa and Size of Lumen*

	No Compression	Compression with			
		Small Lumen	Medium-Large Lumen	Large Lumen	Obliterated Lumen
Chronic group.....	21	10	22	42	8
Control group.....	36	12	11	16	27

operation in these 29 cases varied from 9,900 to 12,300 with an average of 8,640. The neutrophil percentage averaged 66.

The most outstanding morphologic indication of functional disorder in this group of 103 appendixes consisted of obvious compression of the mucosa, particularly in the distal portion of the organ. The compression was shown by shortening of the columnar cells on the surface of the mucosa and shortening and tortuosity of the crypts in the areas involved (fig. 1). In 42 of the 103 appendixes studied the compression of the mucosa was associated with marked dilatation of the lumen and thinning of all layers of the walls (table 1). In the control group in which the appendix was removed at the time of performance of other seemingly more important operative procedures, compression of the mucosa was observed in some of the appendixes. Pronounced degrees of compression and dilatation of lumens were much less common in this group. The control group, which was selected from consecutive cases, was built up until there were as many appendixes having patent lumens in it as were found in the chronic group.

Considerable study of the significance and mode of production of dilatation of appendical lumens has been made by various observers.

Activity of the vagus is said to cause shortening of the organ and constriction of the proximal or ampullar portion of the lumen.<sup>5</sup> The muscularis of this part of the organ is commonly thicker than that of the more distal portions. That spasm of the ampullar portion may be prolonged and promote retention of feces in the distal portion has been demonstrated by roentgenologic studies.<sup>6</sup> Thirty of the 103 appendixes showing chronic inflammation which are discussed in this paper had been examined roentgenologically. Twenty of these remained filled 48

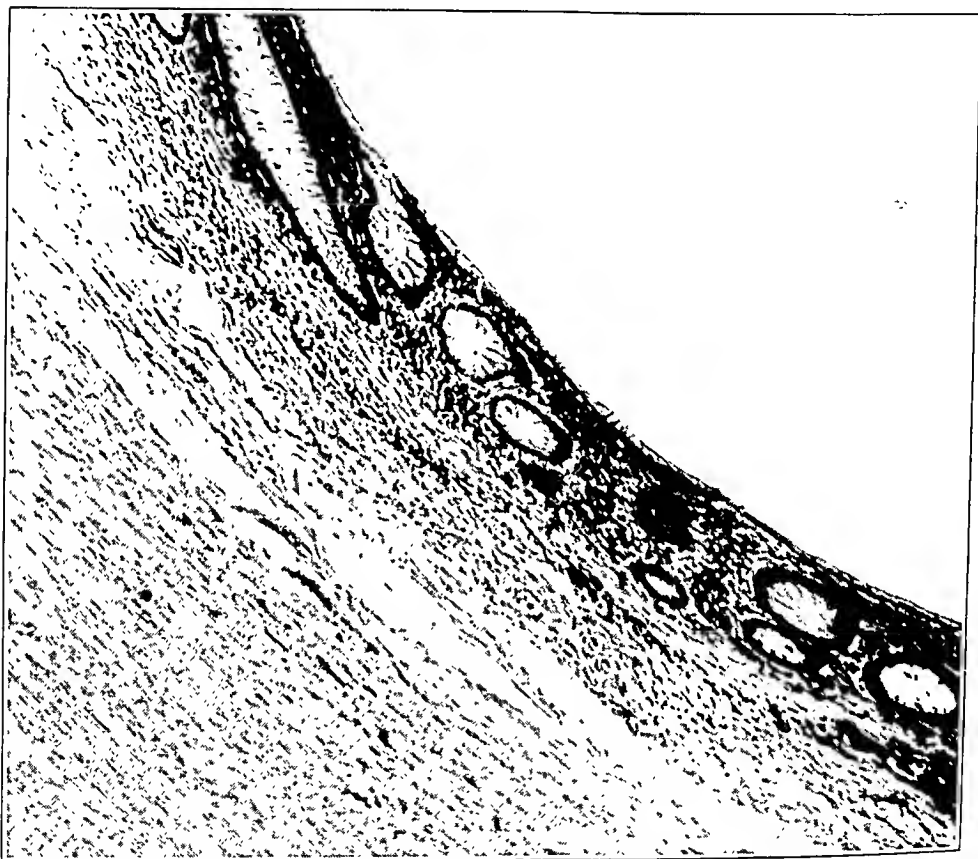


Fig. 1.—Appendix showing thinning of the mucosa and distortion of crypts by compression.

hours or more, and the lumens of 6 failed to fill. One of the 6 was subsequently found to have obliteration of the lumen.

That spasm of the ampulla is not the only factor preventing proper emptying and favoring dilatation of the lumen of the appendix seems evident. Many appendixes showing these changes also presented scar-

5. Westphal, K.: Appendizitis und Kotstein als Folge gestörter Appendixfunktion, *Deutsche med. Wchnschr.* **60**:499 (April 6) 1934.

6. Krenn, L.: Was leistet die Röntgenuntersuchung des Wurmfortsatzes? *Wien. klin. Wchnschr.* **47**:778 (June 22) 1934.

ring and contraction of the submucosa proximal to the dilated portions.<sup>7</sup> Irregular and multiple constrictions were often observed.

It may readily be imagined that attempts to empty themselves on the part of appendixes having functional or mechanical obstruction may result in attacks of pain or appendical colic.<sup>8</sup> It should be recognized that kinks and adhesions or other external causes of obstruction may also cause appendical colic.<sup>9</sup> In the series reported here a large number of the appendixes presenting dilatation of their lumens were more or less mechanically obstructed by adhesions, peritoneal bands and kinks. However, a comparison of tables 1 and 2 shows that a practically equal proportion of the appendixes in which dilatation was slight also presented external causes of obstruction. This leads one to make the suggestion that factors within the appendix such as spasm and scarring may be more important than external causes of obstruction, at least, in many cases. It is to be noted that the latter are more frequently recorded as present in the cases of chronic appendical disorder than in the control group.

TABLE 2.—*Presence of Adhesions, Peritoneal Bands and Kinks*

	With Dilatation	Without Dilatation	With Obliterated Lumens
Chronic group.....	25	14	S
Control group.....	4	5	S

It is easy to believe that a disordered appendix which has difficulty in emptying itself may have reflex effects on other parts of the gastro-intestinal tract.<sup>10</sup> This doubtless explains the nausea and vomiting which are frequently present. In the study of the control series of cases reported in this paper I attempted to correlate the presence of pathologic changes elsewhere along the gastro-intestinal tract with signs of obstruction of the appendix. In the control series there were a number of appendixes which had been removed as a secondary consideration from patients having peptic ulcers or other pathologic conditions of the alimentary canal. Many of these appendixes presented dilated lumens but the number studied was not sufficient to lead to definite conclusions.

7. Williams, B. W., and Boggon, R. H.: *The Mechanics of Appendicitis*, Lancet, **1**:9 (Jan. 6) 1934.

8. Koster, H.: *Chronic Appendicitis*, Arch. Surg. **16**:44 (Jan.) 1928.

9. Bigelow, W. A.: *A Study of Right-Sided Abdominal Pain in So-Called Chronic Appendicitis*, Canad. M. A. J. **23**:22 (July) 1930.

10. Friedrichs, A. V.: *The Etiology and Pathology of Appendicitis*, New Orleans M. & S. J. **87**:20 (July) 1934.



It is, of course, generally recognized that appendical colic is not the only common cause of pain in the lower part of the abdomen in the absence of fever and leukocytosis.<sup>11</sup> The fact that females are practically twice as numerous as males in the group of cases under consideration here bears mention. Rupture of small ovarian cysts may simulate acute appendicitis.<sup>12</sup> It appears probable that in some cases pain might be present repeatedly and simulate appendical colic. The large number of women in this series who were between 19 and 29 years of age when operated on is of interest, as this is a period of life when ovarian activity is pronounced. There were 8 appendixes in the series of 103 which failed to show evidences of obliteration or mechanical or functional obstruction of the lumens. Six of the 8 appendixes were from women who were from 16 to 25 years of age.

A few words concerning appendixes in which the lumens were completely obliterated might be of interest. In the chronic group of 103 appendixes 8 such organs were found. In the control group of 122 appendixes 27 appeared. About each of the 8 appendixes in the chronic group adhesions were found. These may well have been a cause of distress.<sup>13</sup> It seems illogical for a pathologist to censure a surgeon who removes an appendix from a patient who is having acute distress only to find the lumen of the organ closed. Search of the histories of the 35 patients having obliterated appendical lumens failed to be very fruitful in the demonstration of probable previous attacks of acute appendicitis. The average age of the patients when the appendixes with obliterated lumens were removed was 41.4 years.

#### ACUTE APPENDICITIS

Active inflammation could be demonstrated in 119 of the 344 appendixes discussed in this paper. The 119 appendixes may be divided readily into three groups: 77 which were subject to frankly acute purulent inflammation, 8 in which healing processes were in evidence and 34 in which the inflammatory process was mild or early. More detailed attention will be paid the latter group because of its relation to what pathologists have at times chosen to call "chronic appendicitis."

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11. Deal, Don: Non-Surgical Chronic Abdominal Pain, *Illinois M. J.* **65**:149 (Feb.) 1934.

12. Boggon, R. H., and Wrigley, A. J.: Rupture of Ovarian Blood-Cysts Simulating Acute Appendicitis, *Lancet* **2**:1068 (Nov. 14) 1931. Meigs, J. V., and Hoyt, W. F.: Rupture of the Graffian Follicle, the Corpus Luteum and Small Follicle or Lutein Cysts Simulating Appendicitis, *Am. J. Obst. & Gynec.* **25**:532 (April) 1933.

13. Horsley, J. G., and Warthen, H. J., Jr.: The Pathogenesis and Symptoms of Chronic Obliterative Appendicitis, *Ann. Surg.* **96**:515 (Oct.) 1932.

*Frankly Acute Appendicitis.*—A few statistics concerning the series of 77 frankly acute cases will be given briefly. The average duration of illness before coming to the hospital for the patients who recovered was 29.2 hours. Thirteen of the 77 patients died in the hospital, while none of the patients with early inflammation, to be considered separately, succumbed. The patients who died had waited on the average 69.9 hours before coming to the hospital. This long period is in accord with the observations of others.<sup>14</sup> Sixteen of the 77 patients gave histories of previous attacks. The average temperature on entry into the hospital was 99.8 F. Preoperative total leukocyte counts averaged 17,500 with a neutrophil percentage of 84.8. In the fatal cases the figures were 18,733 and 85.4, respectively. In 10 cases the total white cell counts were below 13,000. In these cases in particular the use of the Schilling count proved of aid<sup>15</sup> in indicating that an infection was present. Seventeen of the appendixes contained definite fecaliths and many others contained fecal masses as well as pus. The average age of the patients who survived was 25.46 years, and that of the patients who died, 37.9 years. Five of the fatal cases were in patients over 50 years of age. Four were 14 or less. An attempt was made to correlate the incidence of appendicitis with climatic conditions. Definite observations were not possible, but in each of the years during which the cases occurred the incidence was a little higher in the warmer months.

*Healing Acute Appendicitis.*—Eight of the patients were operated on at a time when the appendix presented indications of the presence of healing. The walls were thickened, but not so much by purulent exudation as by edema and early formation of scar tissue. The latter was present mainly in the serosa and submucosa. The mucosa showed various degrees of repair of ulceration. All layers contained abundant eosinophils. It has been pointed out that eosinophils in the mucosa are not an indication of inflammation,<sup>16</sup> but when present in other layers they signify a healing process. A prolongation of this process might be regarded as a true chronic appendicitis, analogous to the chronic salpingitis which so frequently follows the acute phase of infection of the fallopian tubes. While after acute inflammation has been present healing of the appendix may at times require a few weeks, the process seems very seldom to be retarded as it so frequently is in salpingitis. The possibility of drainage into the cecum before scarring occurs may be the explanation of this fact.

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14. Bower, J. O.: Appendicitis in Philadelphia, J. A. M. A. **102**:813 (March 17) 1934.

15. Warnock, F. B.: Leucocyte Count and Histopathology in Acute Appendicitis, Am. J. Surg. **21**:47 (July) 1933.

16. Butka, H. E.: Chronic Appendicitis, California & West. Med. **26**:467 (April) 1927.

The 8 patients in this group had been ill an average of 11 days before operation. Their temperatures on entry into the hospital averaged 99.1 F.; the white counts, 13,400, and the neutrophil percentage, 72.5. The total white counts varied from 6,800 to 31,000. The two highest counts were on blood from patients having abscesses about their appendixes. All the patients of this group recovered.

*Early or Mild Acute Appendicitis.*—This group of cases, which numbered 34, is of especial interest. Careful consideration of the appendixes brings forth the observation that relatively slight inflammatory changes may be associated with definite clinical evidences of appendical disease. Furthermore, the observation may be made that great variation in the severity of the lesions of acute appendicitis is possible.

Most of the patients in this group were having acute attacks at the time their appendixes were removed. However, in nearly one half of these patients the attacks were so mild that the surgeons considered that they were dealing with exacerbations of so-called chronic appendi-

TABLE 3.—*Temperatures and Leukocytes Counts with Different Types of Appendicitis*

Type of Appendicitis	Preoperative Temperature, F.	Leukocytes	Neutrophil Percentage
Chronic.....	98.6	7,960	59.7
Mild acute.....	99.3	12,900	80.0
Frankly acute.....	99.8	17,500	84.8
Healing acute.....	99.1	13,400	72.5

citis. The reason for consideration of these patients together in one group is the similarity of the pathologic pictures present. This will be discussed again later.

Pain was the most universal complaint of all of the 34 patients. Thirty had nausea and 24 had vomited. Illness had been present for from 3 hours to 5 days before operation. The average duration of complaints before operation was 40 hours. This fact considered with the type of pathologic process present indicates that the disease was present in a relatively mild form in the patients who had been ill more than 1 or 2 days. In some cases the mildness of the lesions found is explained by the early removal of the organ. Eleven patients were ill less than 12 hours before operation, and 9 others had been sick less than 24 hours. A record of previous attacks was found in the histories of 17 of the patients. The average time which had elapsed since the first attack was 3.5 years and the average number of attacks which had been suffered by these 17 patients was 3.

The average temperature recorded on entry into the hospital was 99.3 F. The total leukocyte counts varied from 5,400 to 29,250 with an average of 12,900. The neutrophil percentage averaged 80 (table 3).

In the cases in which the total counts were low attention to the neutrophil percentage and the Schilling count was of definite value in indicating the presence of an infectious process. Ages varied from 6 to 36 with an average of 25.4 years. Eighteen patients were between 20 and 25 years old.

The basis on which this group of cases was selected for separate consideration was the type of pathologic process present. Congestion and edema were observable grossly. In some cases the lumens of the appendixes contained purulent material more or less mixed with feces and mucus. No ulcerations of the mucosa were observable with the naked eye. With the aid of the microscope occasional tiny ulcerations were found. Some of these, as in cases studied by Steinberg, were surrounded by relatively little cellular reaction. Moderate numbers of neutrophils were found in the mucosa. These were usually in small areas which might be missed if only one portion of the appendix were studied. Very few, and in many cases, no leukocytes were found in the outer layers.

Examination of the lymphoid tissue discloses the most readily discoverable indications of early and mild acute inflammation of the appendix. Neutrophils appear in the lymphoid tissue practically as quickly as they do in the mucosa. This frequently renders the lymphoid tissue the easiest place to find indications of mild acute appendicitis. The most readily noticeable feature of the lymphoid tissue in the early lesions is the presence of large phagocytes which have ingested damaged leukocytes (figs. 2 and 3). These cells are found in the germinal centers. Their abundant pale cytoplasm gives the germinal centers a vacuolated or spongy appearance as seen by low power magnification. The presence of these active phagocytes was the most constant indication of acute infection found in the 34 appendixes of this series.

The fact that the infiltrating cells are neutrophils and the absence of scarring indicate that the process described is acute rather than chronic. From a clinical view this conclusion seems rational because of the relatively short duration of the individual attacks of pain and their tendency to be accompanied by elevation of temperature and of the leukocyte count.

By way of comparison a study of the lymphoid tissue of the appendixes of the chronic and control groups was made. In the chronic series of 103 cases, 95 appendixes were found with lumens patent. In 14 of the 95 the lymphoid tissue was practically devoid of germinal centers. Fifty-one appendixes contained germinal centers in which few or no phagocytes were found. In the remaining 29 appendixes active phagocytes were present in the germinal centers but in definitely smaller numbers than in the series of 34 cases just discussed.

The patients whose appendixes presented no germinal centers had an average leukocyte count of 7,260. For the group whose appendixes presented germinal centers but no phagocytes it was practically the same, being 7,790. The 29 patients in whose appendixes the germinal centers contained some phagocytes tended to have higher white counts. These counts varied from 3,600 to 12,300 with an average of 9,500. Thirteen of the counts were above 10,000. Neutrophil percentages varied from 54 to 91 with an average of 66. Seventeen of the 29 patients were

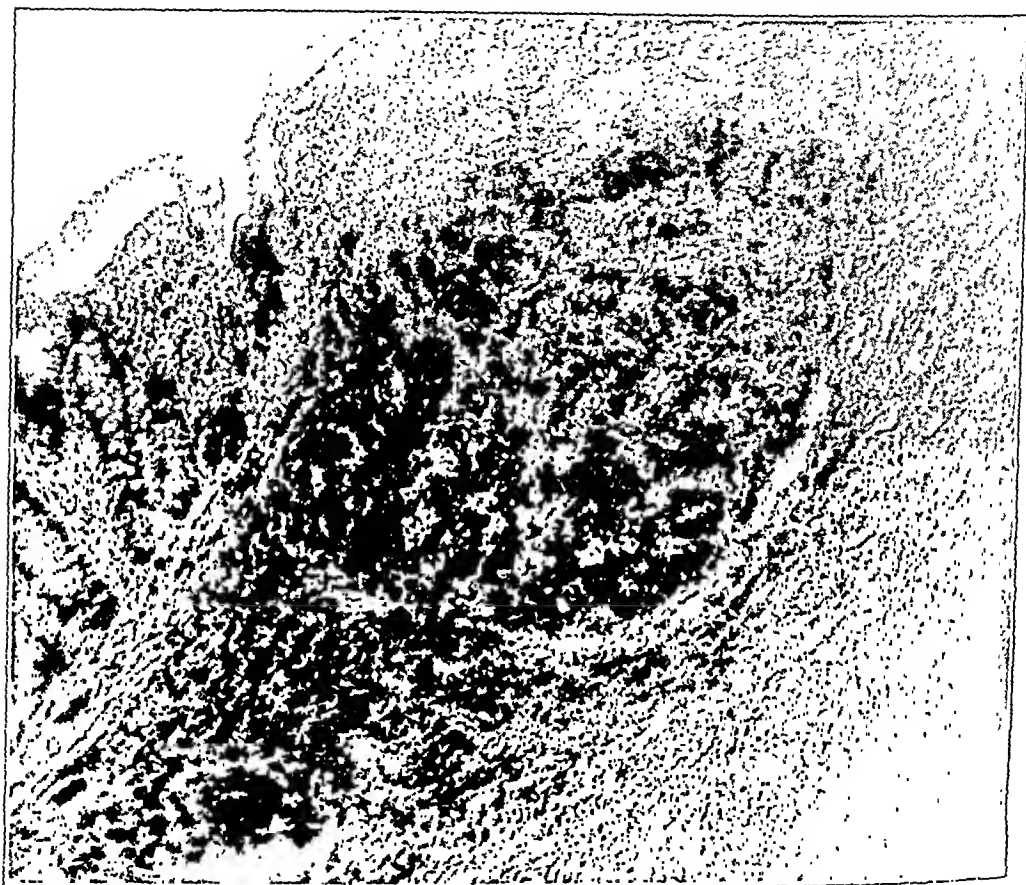


Fig. 2.—Low magnification of a germinal center of the lymphoid tissue of an appendix. Note the active phagocytes having much clear cytoplasm which are scattered in the germinal center.

having acute attacks of pain when operated on. Because of the mildness of the attacks, all were regarded as having only chronic appendicitis clinically. If one accepts the presence of moderate numbers of neutrophils in the germinal centers and the presence of a few active phagocytes as evidence of acute inflammation of mild nature this group is not separable from the series of 34 cases of mild acute appendicitis discussed in the foregoing paragraph. The decision to consider the 29 cases with the chronic group was an arbitrary one based on the fact

that the evidences of inflammation, though present, were slight. The concept that many apparent attacks of chronic appendicitis may be in truth very mild degrees of acute appendicitis appears to me to be worthy of consideration. In many cases of mild acute appendicitis the signs may be so slight that a correct diagnosis is difficult.<sup>17</sup>

The control series of 95 appendixes with patent lumens included 13 in which no germinal centers were found. Seventy-seven presented germinal centers but no phagocytes. In 5 of the appendixes of the control series moderate numbers of active phagocytes were found in

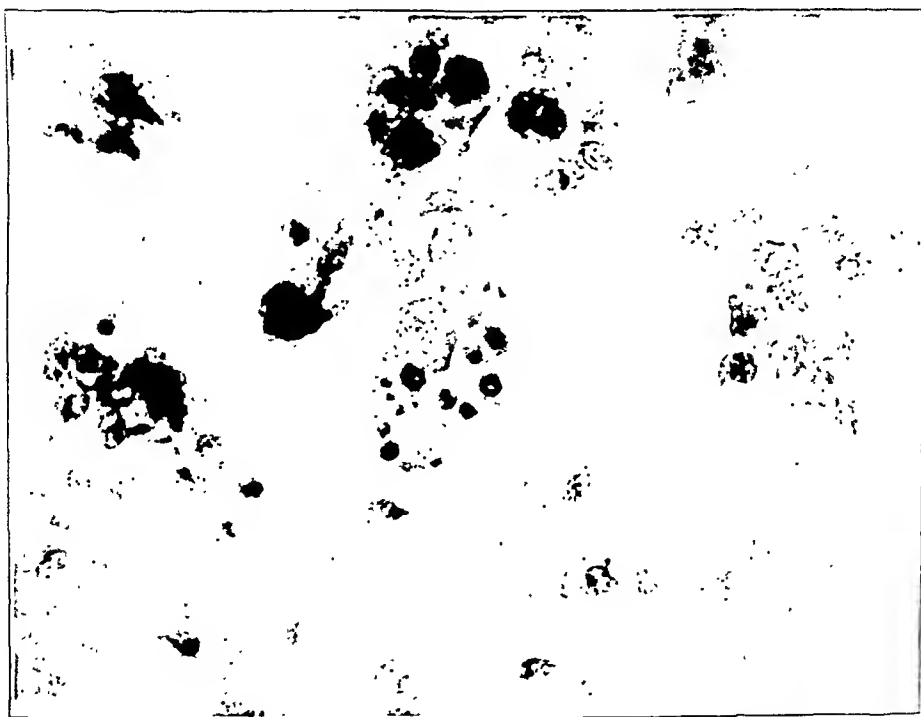


Fig. 3.—High magnification of one of the active phagocytes shown in figure 2. It has ingested fragments of neutrophils.

germinal centers. As the patients were suffering from conditions other than appendicitis for which surgical operations were performed clinical indications of mild degrees of appendicitis were obscured.

The relationship of appendical obstruction to mild acute appendicitis remains to be considered. In the series of 34 appendixes discussed under the heading of mild acute appendicitis 20 presented definite evidences of failure to empty properly. Adhesions or other external causes

17. McClure, R. D.: Chronic Appendicitis, *Ann. Surg.* 94:203 (Aug.) 1931.

of obstruction were present in 8 of the 20 cases. In 14 appendixes evidences of delayed emptying were not recognizable. Of the 29 appendixes considered with the chronic series but in which some active phagocytes were found, evidence of obstruction was present in 20. The conclusion may be made that mild degrees of acute appendicitis frequently occur in obstructed appendixes, but that definite evidences of obstruction may be lacking when mild inflammation is found.

#### SUMMARY

Failure of the appendix to empty properly is a common cause of repeated attacks of pain in the right lower quadrant of the abdomen. The pain is frequently associated with reflex nausea and vomiting. In many cases the cause of obstruction is spasm of the muscularis of the ampulla of the appendix. Elevation of temperature and of leukocyte count appears not to occur unless acute inflammation is also present. Until some better method of relief of obstruction is found the practice of removal of obstructed appendixes is warranted. Appendical colic due to obstruction may be most distressing. Obstructed appendixes are frequently the site of acute inflammation, although this may apparently occur in the absence of marked or long-standing obstruction. When appendical obstruction is the cause of attacks of pain the attacks may be more frequent than when the illness consists of acute appendicitis. Study of the control series indicates that some patients may have appendical obstruction and complain relatively little of it.

Many attacks of acute appendicitis are very mild. The inflammation frequently involves only the inner coats of the appendix. The most easily observed evidence of mild acute appendicitis is the presence of large phagocytes which have ingested leukocytes. These cells are found in the germinal centers of the lymphoid tissue. Repeated mild attacks may conceivably cause thickening of the submucosa and narrowing of the lumen with resultant appendical obstruction. Further attacks may result in obliteration of the lumen. That severe attacks of acute appendicitis are not necessary in order that the lumen may be obliterated is shown by the fact that the outer layers of appendixes in which the lumens are obliterated seldom show very marked scarring.

Since attacks of acute appendicitis are frequently very mild, many are unrecognized. When clinical signs of acute appendicitis are present it is not possible to predict with accuracy the appearance of the appendix at operation. Many appendixes removed early in the course of illness present surprisingly little pathologic change. This may lead to errors of interpretation by pathologists who may accuse surgeons of removal of normal appendixes. Further search in such cases will frequently reveal the indications of early acute inflammation discussed. In other

cases mild acute appendicitis is erroneously diagnosed as chronic appendicitis by the surgeons who operate on the patients. Study of the blood count, particularly the Schilling count, is of definite aid in gaging the severity of the condition. Mortality figures are very low when appendixes are removed while the attacks are still mild. Since it is not possible to predict accurately the course of events in the appendix, early operation is to be urged.

#### CONCLUSION

The vermiform appendix is frequently the seat of chronic or recurrent disease. So-called chronic appendicitis usually consists either of appendical obstruction or of recurrent attacks of mild acute appendicitis.

In making a diagnosis of chronic or recurrent appendical disorder other causes of abdominal pain, such as ovarian changes in the female, must be considered.

The lesions produced by mild acute appendicitis may be so slight as to be readily overlooked on examination of the organ.



# PILONIDAL SINUS

## SURGICAL TREATMENT AND PATHOLOGIC STRUCTURE

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It is our purpose in this paper to present the clinical and pathologic data on which are based our views on the treatment of pilonidal sinus. The question of etiology, though unsettled, will not be considered here. The clinical picture is a familiar one, and its description needs no repetition. The conception of the disease on which most surgical treatment is based, however, will be discussed at some length.

### CURRENT CONCEPT OF MORPHOLOGY

It has been commonly believed that the presence of a recurrent or persistent sinus after excision implies that some of the diseased tissue must have been left behind. This belief has naturally led to increasingly radical excisions in an attempt to remove all the diseased tissue at one operation. The frequency of recurrence and persistence of the sinus in spite of such operations has given rise to the impression that a pilonidal sinus consists of a complex network of ramifying branches of unknown extent. This concept has been strengthened by the appearance often produced when methylene blue or another dye is injected into the sinus. Fine tubular structures filled with dye have been regarded as radiating branches of the pilonidal sinus system.

### TREATMENT BASED ON CURRENT CONCEPT

The radical excisions resulting from this concept have led to new problems. The novice finds it difficult to resist the temptation to perform an immediate midline closure of the skin. The dead space formed by such a closure invariably fills with clotted blood, which may or may not become infected, the result being usually a broken-down wound, a persistently draining sinus or both. The partial closure of the wound with the inclusion of a drain leads to the same result. Although it is now commonly recognized that many sinuses so produced contain no hair or other epithelial elements and are in reality artefacts resulting

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from a combination of dead space and chronic infection, the problem they present is as troublesome as if they were true recurrences.

It is chiefly toward meeting this and other difficulties growing out of the acceptance of an original radical excision that the ingenuity of investigators has been directed. Their efforts are all variations of two main plans: (1) to keep the wound open either by packing or irrigation until it has granulated in from the bottom and (2) to close the wound completely either by deep sutures or by a plastic flap in the hope that no dead space will develop as a result of sepsis, tension or formation of hematoma.

#### FIRST SERIES: RESULTS

In the series of cases previously reported by one of us<sup>1</sup> treatment was based on these principles. The results are given in table 1. (For the sake of convenience no distinction is made here between true and pseudo-recurrences.) Primary closure by any method gave a rate of recurrence of 36 per cent in twenty-eight cases in which the results of

TABLE 1.—*Results of Radical Excision in the First Series*

Results	Number of Cases	Percentage of Recurrence
Primary closure.....	23	36
Partial closure.....	24	50
Open packing.....	46	15
Combined.....	95	30

operation were known; partial closure, a rate of 50 per cent in twenty-four cases, and open packing, a rate of 18 per cent in forty-six cases—the total rate of recurrence was 30 per cent in ninety-eight cases in which information as to the results of operations was obtained.

When the cases in which radical operations had been performed previously were separated from those in which no such operation had been performed the rate of recurrence, as would be expected, was found to be much higher in the first group, amounting to 100 per cent for primary closure, 88 per cent for partial closure and 58 per cent for packed open secondary procedure, as compared with 31 per cent for primary suture, 31 per cent for partial closure and 3 per cent for packed open original procedure or a gross rate of recurrence for secondary procedure, by whatever method, of 76 per cent, as opposed to 19 per cent for original operations.

The average patient in this series lost eight and seven-tenths weeks from work, spent ten and nine-tenths postoperative days in the hospital and made nine and seven-tenths return visits for each radical operation. Among those who were cured, the average time required for the wound

1. Rogers, H.: Pilonidal Sinus, Surg., Gynec. & Obst. 57:803, 1933.

to heal was two and seven-tenths months. Thirty-nine per cent had residual symptoms referable to the scar. Only 57 per cent of the traced patients rated the result of their operation as excellent or good.

In short, from an analysis of this series and a review of the literature it was clear that the current methods of treating pilonidal sinus were peculiarly unsatisfactory, and a suspicion arose that perhaps the fault lay in a fundamentally wrong conception of the underlying pathologic process. To investigate this possibility it has been necessary to continue to perform radical block excisions in order to secure material for study of the pathologic process. This we have now done in sixty-two additional cases.

#### SECOND SERIES: DETAILS OF TREATMENT AND RESULTS

In the study of this second series two objects have been kept in view. One was to learn something about the pathologic process underlying the condition and the other was to find out whether the ill success of treatment was due to faulty technic or was inherent in the methods used.

TABLE 2.—*Results of Radical Excision in the Second Series*

Results	Number of Cases	Percentage of Recurrence
Primary closure.....	13	33
Partial closure.....	1	100
Open packing.....	20	25
Combined.....	43	34

Forty-four surgical specimens were studied and will be described presently in some detail. Seventy-two radical operations and one sclerosing procedure were performed.

*Radical Excision (Table 2).*—In order to minimize sepsis no radical operation was performed in the presence of acute inflammation. Abscesses were drained and allowed several weeks of treatment in the outpatient department to become quiescent. Before excision at least twenty-four hours were allowed for preoperative cutaneous preparation. Castor oil was given the day before and a cleansing enema the morning of operation to minimize postoperative contamination of the wound. All excisions were performed under general anesthesia to avoid the possibility of spreading infection into sound tissue by the injection of a local anesthetic. With the patient in the prone position the main orifice of the sinus was identified, and all other orifices were closed with sutures or clamps. A sterile solution of methylene blue or a suspension of india ink was forcefully injected into the main orifice. A symmetrical block excision was then performed with a knife, the line of excision was kept outside of all stained tissue, or, if this failed, whatever stained tissue could be seen was removed piecemeal. In each case an ellipse of skin equal in width to the widest extent of the underlying cavity was removed. This was done to insure against the formation of a dead space during healing.

*Primary Closure.*—Primary closure was considered only (1) if the operation was an original procedure, (2) if no gross sepsis or contamination was present,

(3) if satisfactory extirpation of the diseased tissue had been achieved and (4) if hemostasis had been perfect. Depending on the size of the defect to be closed either a midline closure with undercutting at the full depth of the fat or the plastic flap method described by Lahey<sup>2</sup> was then used. Great care was taken to obliterate all dead space and prevent undue tension on stitches by an adequate mobilization of tissues. After the operation the patient was kept in the prone or lateral position for at least eight days. The bowels were kept closed for six days by means of deodorized tincture of opium and a restricted diet. The patient was kept in bed for at least ten days and in the hospital for fourteen days.

A total of six patients with obviously circumscribed lesions had their defects closed by simple undercutting and suture in the midline. In two the lesions failed to heal and further surgical intervention was required for persistent draining sinuses. Two lesions were unhealed at the end of two months and four months, respectively, when the patients were lost sight of. Two healed by first intention.

Twelve primary closures were performed by the plastic flap method. Seven wounds healed by first intention while the patients were in the hospital, but three of these later broke down, one requiring reoperation, and the other two each requiring four months to heal permanently. For four others the subsequent developments were as follows: Two wounds were in patients in whom the results were not traced; one patient complained of numbness and tingling in the wound, rating her result good but not excellent, and the fourth patient is free from symptoms with a result she considers excellent. In four patients septic wounds developed during the period of hospitalization. One is untraced; in one the wound healed in three and one-half months; in one it healed in four months, and the fourth required another operation at the end of six months. In one patient a large hematoma developed during the period of hospitalization and required reoperation at the end of six months.

In thirteen traced cases of primary closures there were five recurrences requiring reoperation, and in only two cases were excellent, in five, good, and in one, fair, results reported, as rated by the patients themselves. Since more than the average amount of care was taken in the selection, surgical treatment and management of these thirteen patients, it seems fair to conclude that the ill success was inherent in the principle of primary closure.

*Partial Closure.*—Only one wound of radical excision was partially closed in this series. Reoperation for persistent draining sinus was necessary ten months later.

*Open Packing.*—All wounds which did not meet the rigid requirements for primary closure were packed wide open with plain or iodized gauze. An attempt was made to have each defect saucer-shaped in order to favor healing from the bottom without dead space. To avoid postoperative contamination the patient was kept in bed, in the prone or lateral position, for four days, during which time the bowels were kept closed. The patient was kept in the hospital for from six to ten days. Thereafter the dressings were cared for by a district nurse daily and by a surgeon of the outpatient department at least once a week until the wound was healed or until a persistent sinus requiring reoperation became established. In this series, as in the previous one, the dressings applied in the outpatient department consisted mostly of repacking the cavity and of touching exuberant granulations with silver nitrate. Nothing in the nature of minor surgical intervention was attempted.

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2. Lahey, F. H.: Surg., Gynec. & Obst. 48:109, 1929.

Of fifty-two cases of radical excision in which the method of open packing was used, no results are available for twenty-three as either the wounds are too recent for the purposes of this report or the patients are not traced. In the twenty-nine traced patients there were seven recurrences and twenty-two cures, a rate of recurrence of 25 per cent. The economic loss as measured by hospitalization, return visits, etc., was no lower than that mentioned for the previously studied series (table 3).

It will be remembered that for the group in which the open packing method was used in the first series the rate of recurrence was considerably lower than 25 per cent. We believe that this difference can be accounted for by the fact that the patients in the first series were observed for seven years, during which many persistent sinuses had time to heal spontaneously, whereas in the second series the patients with persistent sinuses have been observed for too short a time to ascertain how many sinuses will eventually close. It is important to note that postoperative sinuses are capable of closing spontaneously after having persisted for as long as two years. For example, eight of the patients in the first series were advised by surgeons of the outpatient department that the sinuses required

TABLE 3.—*Comparison of Results and Economic Losses Following Radical Excision in Two Series of Cases*

Postoperative Data	First Series	Second Series
Gross rate of recurrence.....	30 per cent	34 per cent
Cured patients free from residual symptoms.....	61 per cent	56.3 per cent
Result called excellent or good by patients.....	57 per cent	66 per cent
Average postoperative period of hospitalization.....	10.9 days	13.4 days
Average time to heal.....	2.7 months	3.5 months
Average number of return visits.....	9.7	10.9

reoperation as they had failed to heal in respectively four, five, five, five, eleven, twelve, twenty, and twenty-four months after radical excision, but all these patients refused reoperation. Of eight persistent sinuses all but one eventually closed spontaneously. We believe it likely that enough of the persistent sinuses in the second series will also close spontaneously to make the rate of recurrence in the two series about the same.

*Comment on Results of Radical Operation.*—From a comparison of the results so far obtained in our second series with those obtained in our first series, in which a similar method of treatment was used but the cases were not so well controlled (table 3), it is apparent that no great improvement can be expected. By any of the methods which include radical excision in one stage the economic loss is bound to be considerable, and measures designed to lessen the economic loss, such as closure by suture, serve only to increase the danger of failure. The fact that thirty-two of the operations in the second series were performed by one of us and the other forty were performed by resident members of the staff under his supervision satisfies us that the poor results cannot be ascribed wholly, if at all, to faulty operative technic. We are further convinced that the after-care of the wounds treated by radical excision, with the exception of such primary closures

as heal solidly by first intention, is not adequate as carried out at present in the general surgical outpatient department of a large hospital, and we doubt whether it could be made so. We believe that the task assumed by the surgeon who performs a radical excision is only half accomplished while the wound remains unhealed and the patient uncured. The corollary is that the original operator should personally carry out the after-care of each patient. This could be, and is, done in private practice with some degree of success, but we believe that it is not feasible in hospital practice.

From these considerations we conclude that the high rate of recurrence and the considerable economic loss involved in the treatment of pilonidal sinus by the methods described are inherent in those methods.

*Sclerosing Solutions.*—The suggestion has appeared in the literature that radical excision might be avoided by injecting caustic or sclerosing materials in the hope of destroying the epithelial elements of the sinus and hair nest. On theoretical grounds we believe that such a procedure could succeed only in transforming a pilonidal sinus into a persistent scar tissue sinus presenting the same problems as pseudorecurrences following unsuccessful operative measures. In practice alternate injections and curettings are required, with occasional excisions of devitalized skin, so that the procedure assumes the aspect of a radical excision by combined chemical and surgical means.

The one patient in our series treated by this method was subjected to three injections of sclerosing solution, three débridements of slough and four administrations of gas anesthesia over a period of eighteen days in the hospital. He made twenty return visits, and at the end of six months he had a mutilating scar with a persistent draining sinus under it and refused further treatment.

#### PATHOLOGIC STUDY

This study was undertaken with the purpose of observing and recording the morphology of the sinus tracts and the associated manifestations of infection, determining the probable cause for the recurrence or persistence of symptoms in the specimens obtained at secondary excisions and evaluating the use of dyes injected preoperatively.

#### METHOD OF STUDY

The intact specimen from the operating room was immediately fixed in a dilute solution of formaldehyde, U. S. P. (1:10) for at least twenty-four hours. Parallel longitudinal slices of the entire specimen beginning in the midline were made at intervals of from 2 to 3 mm. Each cut surface was carefully scrutinized under a strong light with a hand lens. Numerous paraffin sections were made from normal-appearing regions as well as from obviously diseased parts.

## CLASSIFICATION AND DESCRIPTION OF TRACTS

The tracts were classified as follows:

	Number
1. Midline tracts	
(a) With a single opening.....	11
(b) With two separated openings.....	8
(c) With multiple openings.....	7
(d) Dimples .....	5
	—
	31
2. Tracts extending laterally from the midline	
(a) With a single midline opening.....	1
(b) With midline openings and one lateral opening.....	5
(c) With a midline opening and multiple lateral openings...	1
	—
	7
3. Unclassified tracts	
(a) "Recurrent" .....	3
(b) Of undetermined structure.....	3
	—
	6
	—
Total .....	44

1. *Midline Tracts*.—In thirty-one, slightly over 70 per cent, of the specimens, the tracts were confined to the midline with no lateral extensions. The variations in their form are diagrammatically presented in figure 1.

(a) *Tracts with a Single Opening* (figs. 1, *A 1* and *A 2*): There were eleven of these tracts. All were surprisingly similar, extending inward and upward; they contained sebaceous material, débris and nearly always hair. The variations were in length, depth and degree of infection. The average length was 4 cm.; the actual length ranged from 1 to 7 cm. Only one tract measured 7 cm., and this extended to a point well over the sacrum and ended in an abscess cavity. The depth ranged from a few millimeters below the skin to a few millimeters above the coccygeal fascia. All were infected but, except for the long tract mentioned, not markedly so. The total diameter of involved tissue never exceeded 1.5 cm.

Microscopic sections revealed in most cases a fairly well demarcated zone of acute and chronic inflammatory tissue walled off by dense fibrous tissue. When epithelium was present it usually occurred in clumps of squamous cells, taking no definite form. In a few sections, however, the epithelium was nearly intact, consisting of many layers of squamous cells with cornification and a prominent granular layer. Formation of rete pegs was marked, and hair follicles with an occasional sebaceous gland were located much as they are in normal skin (fig. 4). The caliber of these epitheliated tubes was small as compared to that of the surrounding inflammatory tissue. Two tracts of this group consisted essentially of epithelium-lined cysts full of sebaceous material and coiled hair.

(b) *Tracts with Two Separated Openings* (fig. 1, *B*): Eight of these midline tracts had two discrete openings more than 2.5 cm. apart. In each of these the tract extended directly from one opening to the other.

(c) *Tracts with Several Openings* (fig. 1, *C 1*): Seven midline tracts were of this type. The abnormal tissue in none of these extended more than 1 cm. above the uppermost opening. Grossly a few appeared to consist of several separate

sinus tracts, but microscopic examination showed that they were connected by inflammatory and scar tissue (fig. 1, C 2).

(d) Dimples: There were five specimens having no actual tract other than an apparently completely epithelialized indentation of the skin in the midline. Sections of these revealed that in all there was some degree of infection in the subcutaneous tissue at the base of the dimple. Beneath one there was considerable scar tissue, suggesting that a fairly extensive infectious process had existed previously. The base of another dimple was within 0.5 cm. of the tip of the coccyx, which was

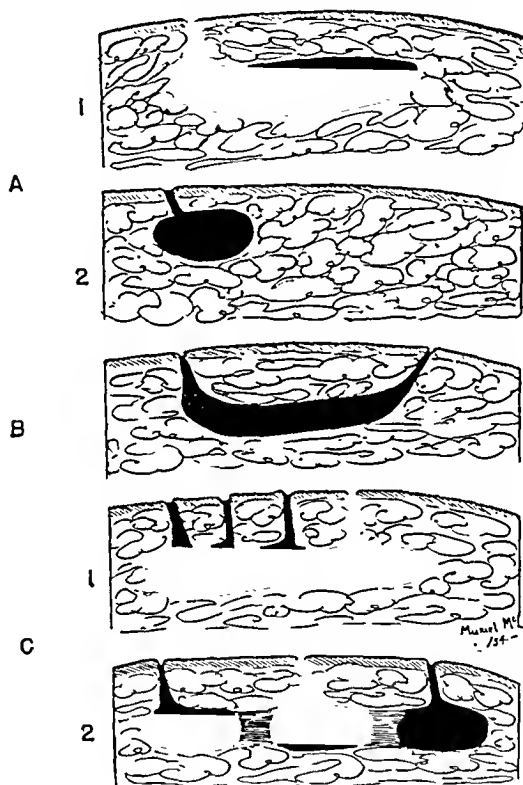


Fig. 1.—The variations of the midline tracts. The diagrams represent longitudinal sections, the upper end being depicted by the part toward the right. A 1 is a simple tract with single opening; A 2, discrete cyst with single opening; B, midline tract with two separated openings; C 1, midline tract with multiple openings; C 2, midline tract with multiple openings appearing grossly to be three separate tracts but seen microscopically to be connected by scar tissue.

removed with it. Microscopic sections showed no suggestion of a fibrous cord or vestige of a communication with neural canal.

2. *Tracts Extending Laterally from the Midline* (fig. 2).—Seven, or approximately 15 per cent, of the tracts were of this type.

(a) *Tracts with Single Midline Opening* (fig. 2, A): One tract had a single midline opening and externally was not distinguishable from similar midline tracts.



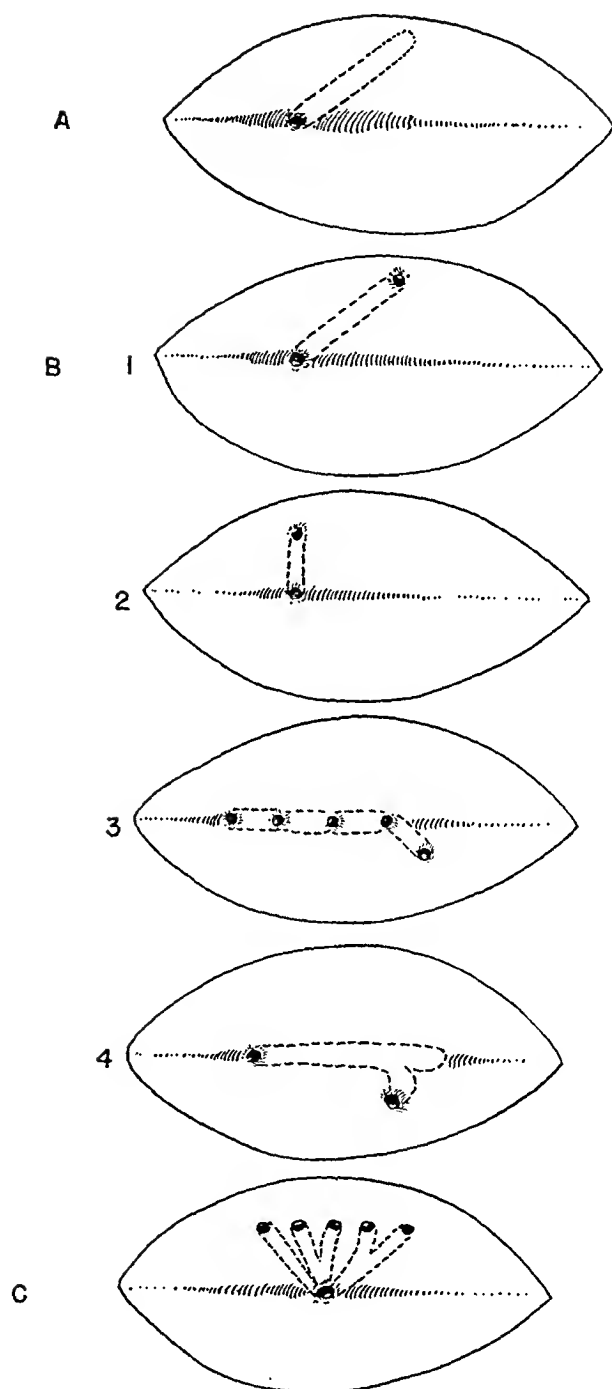


Fig. 2.—The variations of the tracts extending laterally. The diagrams are as viewed from above, the upper end being depicted by the part toward the right. *A* is a tract with single opening extending obliquely; *B 1*, oblique tract with lateral opening; *B 2*, lateral tract with lateral opening; *B 3*, midline tract with multiple openings having a lateral extension with opening; *B 4*, midline tract with a single opening having a lateral extension with opening; *C*, tract with single midline opening communicating by ramifications with five lateral openings.

On section, however, it was found to extend obliquely toward the left so that its upper pole was approximately 1 cm. lateral to the midline.

(b) Tracts with Midline Openings and One Lateral Opening (fig. 2, B 1 and B 2): There were five such tracts, three of which extended directly from one opening to the other with no other extensions. The other two were apparently midline tracts with lateral extensions (fig. 2, B 3 and B 4).

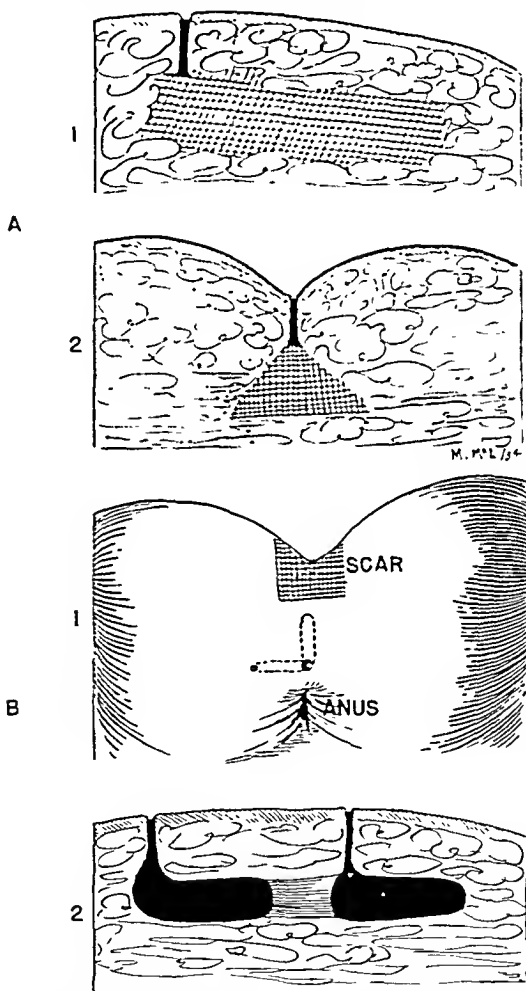


Fig. 3.—The findings in the specimens from secondary resections. A 1 is a longitudinal section, the cross hatching representing chronic inflammatory tissue; A 2, cross-section of same specimen; B 1, diagrammatic representation of the anatomic position of the primary operative scar and the portion of the tract which was overlooked; B 2, reconstructed longitudinal section of what probably was present, the first resection including only the portion to the right.

(c) Tracts with Midline Opening and Multiple Lateral Openings (fig. 2, C): One specimen contained a branching tract leading to five lateral openings. In this

case the extensions were all epitheliated and surrounded by marked inflammatory and scar tissue (figs. 5 and 6). No hair follicles could be demonstrated either in these or in the lateral extensions of the tracts in the foregoing group. The skin about the lateral openings was raised and irregular, and its epithelium was bluish.

3. *Unclassified Tracts*.—The tracts in this group numbered six.

(a) "Recurrent" Tracts: There were three specimens from secondary excisions. Two of these had single sinus openings situated at the lower end of the

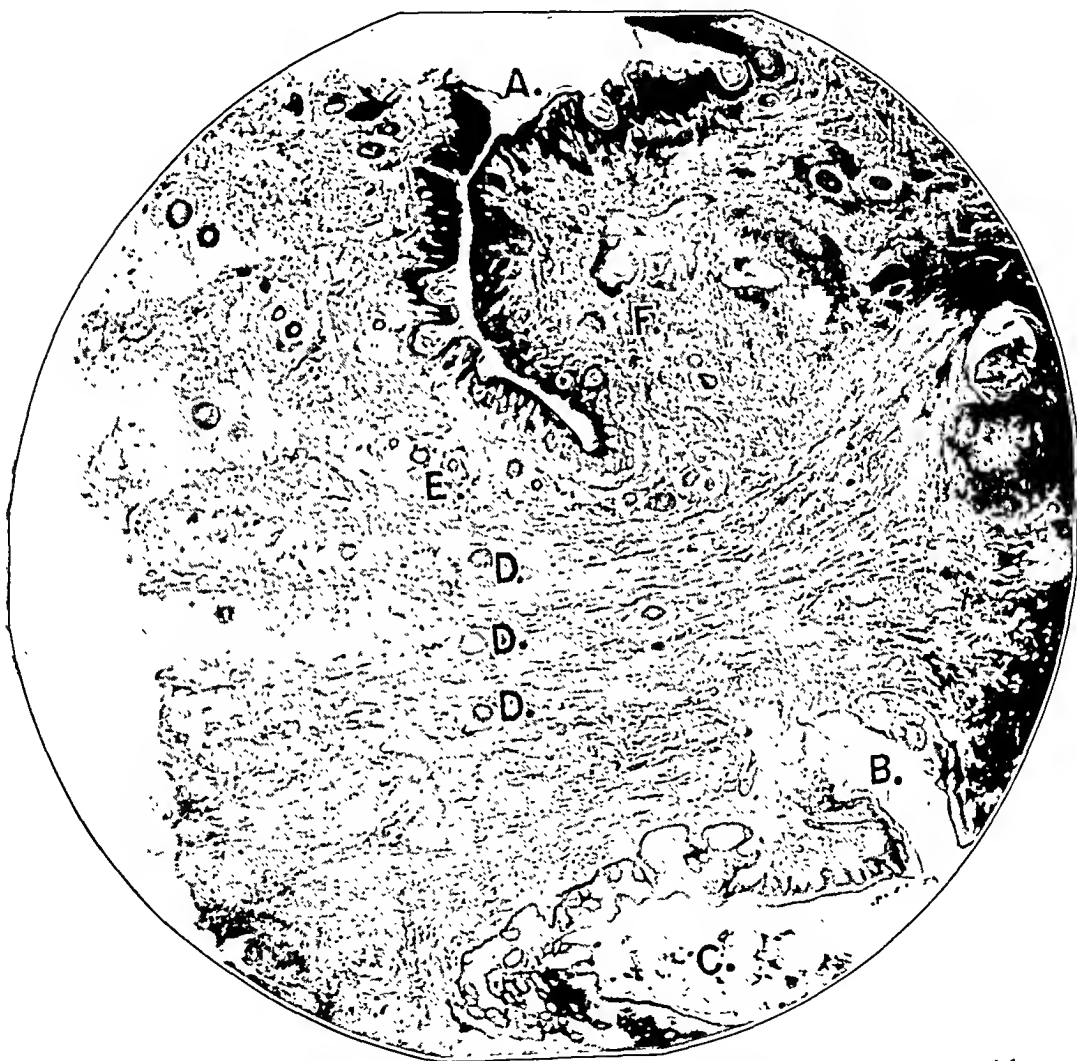


Fig. 4.—Low power photomicrograph of a longitudinal section of a fairly well preserved sinus tract. The upper end is toward the right. *A* is the cutaneous opening of the sinus which follows a tortuous course ending at *B*, where it enters the main tract, *C*; *D*, hair follicles associated with the tract; *E*, a sebaceous gland; *F*, a bit of epithelium apparently isolated by the surrounding chronic inflammatory tissue.

old scar. The epithelium extended deeply, ending in inflammatory tissue in which no epithelium or hairs were found (fig. 3, *A* 1). In both the abnormal tissue on cross-section was roughly triangular (fig. 3, *A* 2), suggesting that it had been

formed by faulty closure or healing—the retention of infected “dead space.” The third (fig. 3 *B*) was interesting because it was really not a recurrence but a portion of the tract which was overlooked at the first operation. Two small openings were found considerably below the scar, one in the midline and one lateral to it. There were a central hair-filled and partially epithelialized tract extending upward to a point near the tip of the coccyx and a small lateral extension with no epithelium and surrounded by scar tissue. The primary operation was performed at this

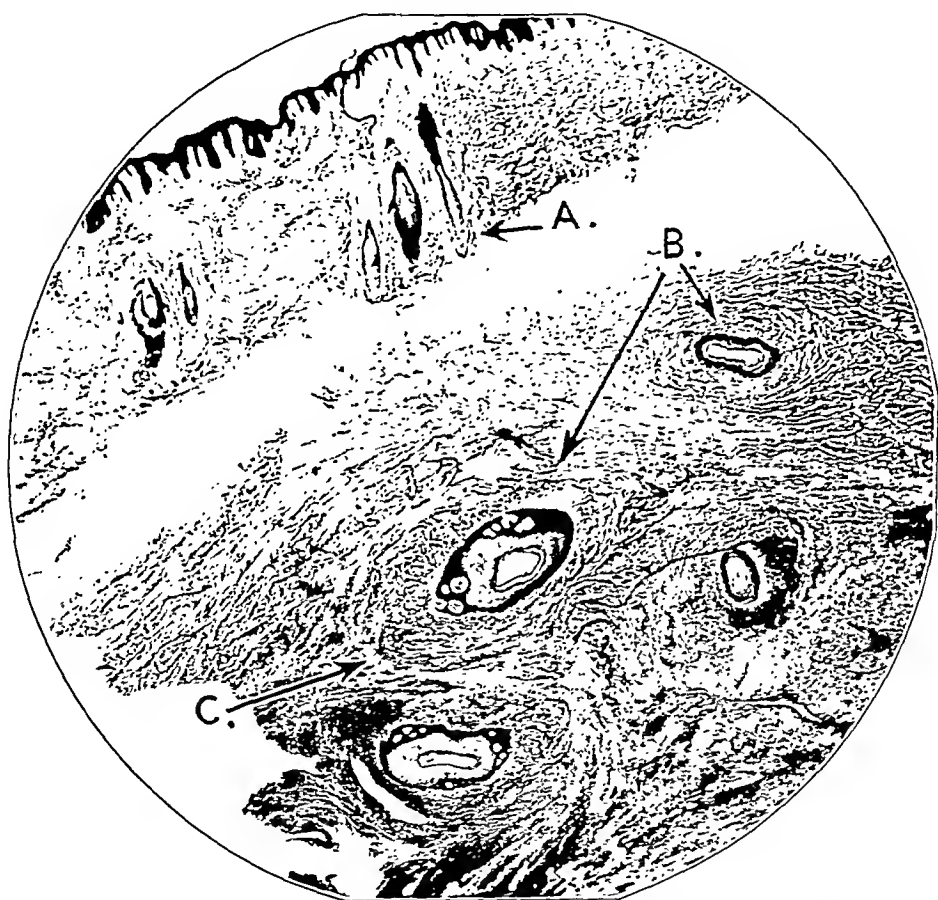


Fig. 5.—Low power photomicrograph of four of the five ramifying tracts depicted in figure 2 *C*. *A* are hair follicles associated with the skin; *B*, epithelialized tracts; *C*, inflammatory tissue. (Note the absence of hair follicles.)

hospital only three months before, and the report on the original specimen is included in this series. The fact that the first specimen contained no epithelium or hair and had but a single opening leads to the belief that possibly this part at one time was continuous with the lower sinus tract, the two portions becoming separated by scar tissue (fig. 3, *B* 2). The error in diagnosis was made probably because the drainage from the upper opening was most marked and the lower openings were distinctly nearer the anus than usual.

(b) Tracts of Undetermined Structure: The structure of the tract in these specimens was undetermined. One specimen, which was mutilated by a previous incision and drainage, is included for other reasons and will be referred to in a subsequent paragraph. Another was received piecemeal and is best described by the operative note: "The tract was extensive, extending downward toward the anus and laterally into the gluteal fibers. A hair nest was found measuring 1 cm. in diameter at a point 3 cm. to the left of the midline and partially within

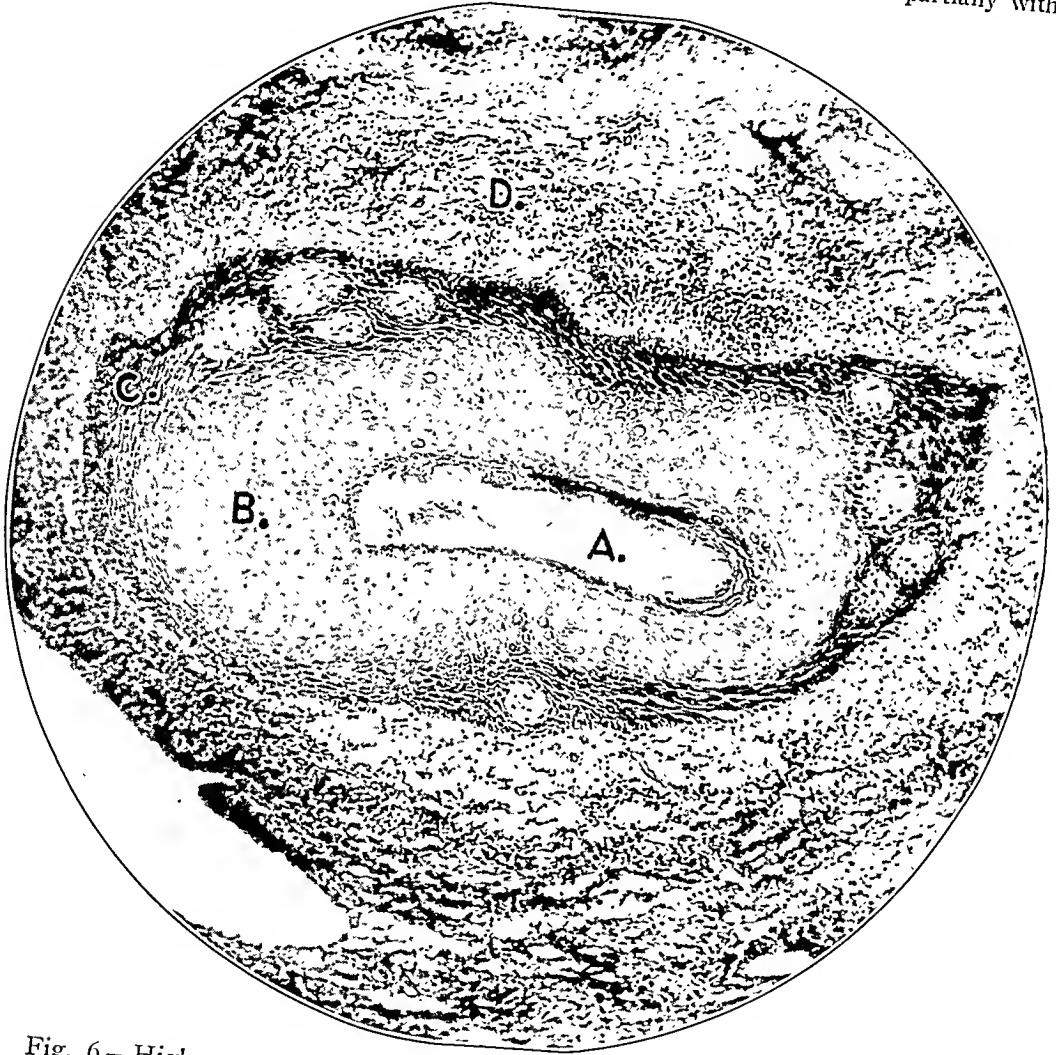


Fig. 6.—High power photomicrograph of a cross-section of one of the tracts shown in figure 5. *A* indicates the lumen; *B*, squamous epithelium; *C*, granular layer; *D*, chronic inflammatory tissue.

the gluteal fibers. The tissue about the anus which was stained with dye was removed." This also will be discussed later.

The third specimen appeared to be a simple dimple, but microscopic examination revealed two discrete clumps of squamous epithelium some distance below the base of the dimple (fig. 7). In multiple sections no suggestion of a lumen or connection with the surface was found. These clumps were surrounded by dense scar

tissue with only slight cellularity. It is possible that this condition represented a sinus tract which had almost completely healed and that the cell clumps were all that was left of the old tract.

#### INJECTION OF DYES

Into twenty-four of the specimens an aqueous suspension of india ink (1:40) had been injected before the operation. This suspension was chosen because it

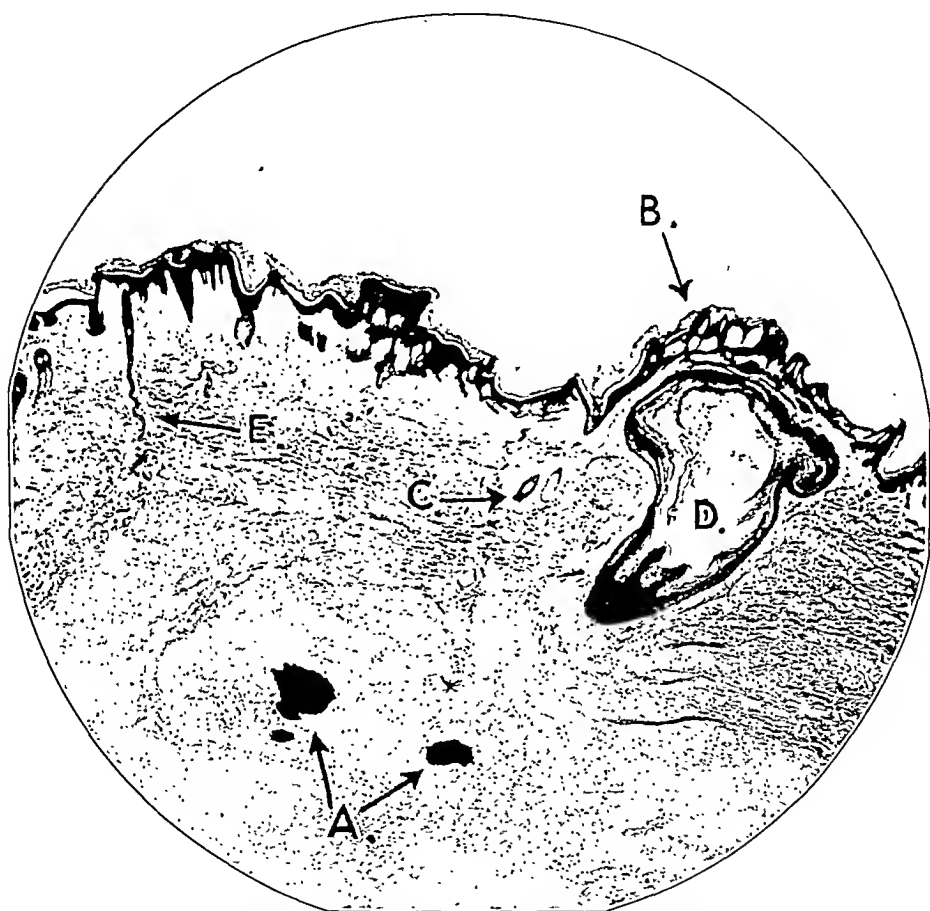


Fig. 7.—Low power photomicrograph of a dimple. *A* shows isolated clumps of squamous epithelium surrounded by comparatively acellular scar tissue; *B*, the location of the orifice of the dimple, not included in the plane of this section; *C*, hair follicle; *D*, epitheliated dimple; *E*, coil gland.

was not dissolved or disseminated by the fixing solutions and could be visualized microscopically as well as grossly. (For specimens into which methylene blue was injected the procedure was altered to omit the primary fixation in formaldehyde. The examination in respect to determining the location of the dye even

then was unsatisfactory, as the color was easily spread.<sup>3</sup>) The injections were made in the usual manner, the surgeon inserting the tip of a 2 cc. syringe into the main opening after accessory openings were closed by suture or with a specially devised clamp. There was no control of the exerted pressure.<sup>3</sup>

The aforementioned specimen which had previously been incised included several bits of ink-stained tissue which were removed from about the rectum. The ink had been injected into what was believed to be a sinus tract, and the operation

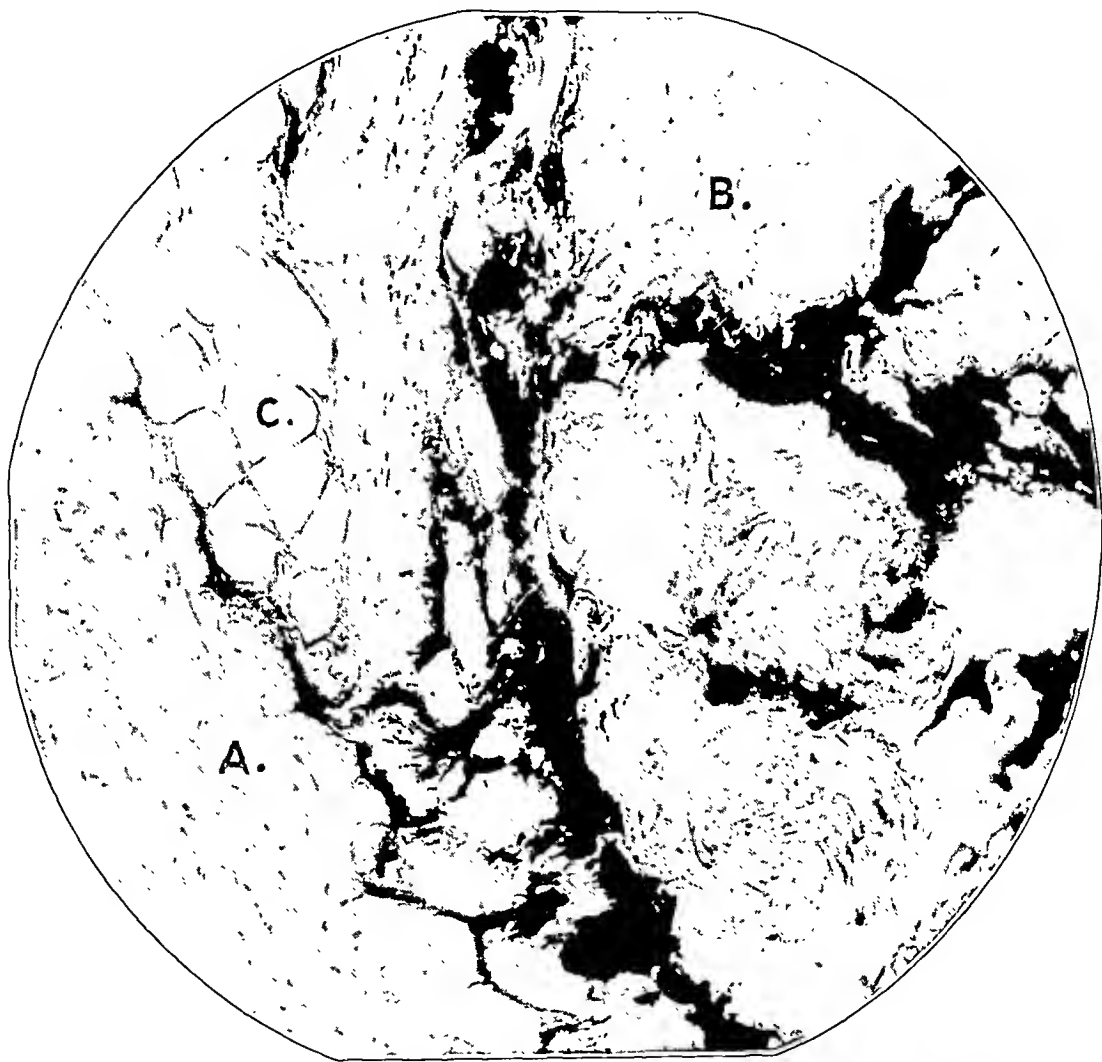


Fig. 8.—High power photomicrograph showing india ink in normal lymphatics. *A* is longitudinally cut muscle; *B*, muscle cut in cross-section; *C*, fat.

became extensive. Microscopic sections of these bits of tissue revealed no evidence of epithelium or inflammatory tissue in the tract, but ink was clearly seen

3. It was originally thought that the ink-filled tracts could be visualized if the surrounding tissue was made transparent by means of a fat-clearing technic. Several specimens were cleared, but it was soon learned that blood vessels filled with changed blood could not be distinguished grossly from tracts containing ink. As several weeks were required to accomplish the clearing and then a supplementary microscopic examination was necessary, this method was abandoned.

in the lymphatics (fig. 8). The statement in the operative note on the other specimen previously mentioned describing the tract as extending downward toward the anus becomes less significant when this possibility is known. Unfortunately, the extra bits of tissue from this specimen which might have been confirmatory if examined were lost in transit to the laboratory.

In three instances the coccyx was removed when the ink stained the coccygeal fascia. Sections, however, failed to show evidence of pathologic changes within the fascia or the bone. In other specimens ink had penetrated normal tissue for

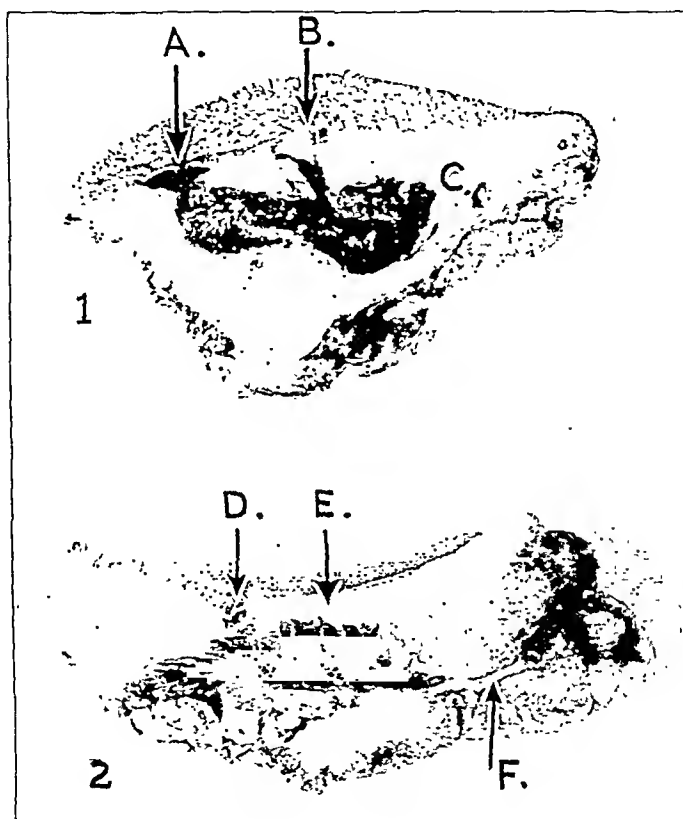


Fig. 9.—Photograph of two specimens after injection of india ink. (The upper end is at the right side.) In 1 is seen a midline tract well filled with ink. *A* indicates the main opening; *B*, an accessory opening; *C*, dense scar tissue. The second specimen, 2, shows a dimple with underlying infection into which the ink has been injected too forcefully. *D* indicates the orifice of the dimple; *E*, finger-like projections toward the skin; *F*, the line of cleavage. (Note that the ink-stained area in this specimen is surrounded by normal fat.)

small distances about the sinus tracts, and in some the ink only partially filled the tracts themselves.

Figure 9 shows two specimens into which ink was injected; one represents a successfully filled midline tract; the other, a dimple with underlying infection in which the injection was made too forcefully. This error supplies a significant



picture. The ink has penetrated for the most part upward and roughly takes the form of a true sinus tract. The finger-like projections toward the skin suggest the mode of formation of the secondary openings in infected tracts. The line of cleavage running upward, so obviously shown in this specimen, was not apparent in the other specimens of dimples.

#### COMMENT ON PATHOLOGIC CHANGES

This study discloses several points of interest to the surgeon.

1. The most important are the observations relating to the preoperative injection of dyes into the tracts. This procedure has been used with varying favor for many years, and although it is not believed to be a perfect guide for the surgeon it has been considered of value. The study of the specimens of this series into which injections of dye had been made suggests that the use of dyes is dangerous if not definitely contraindicated. When a suspension of india ink was used it was frequently found that the particles of ink were forced into normal tissue, leading to much more extensive operations than necessary, and that the actual sinus tract was not always completely filled. Although the study of the specimens into which methylene blue had been injected was unsatisfactory, it is reasonable to believe that this fluid, being a true solution, may penetrate normal tissue to an even greater extent than does the suspension of ink. Furthermore, methylene blue not only fills spaces but colors the tissues themselves. When any coloring matter is present the operation necessarily becomes one of removing all stained tissue, for it is practically impossible grossly to differentiate between normal and abnormal tissue when both are stained alike. Only when the entire tract and nothing else is filled can the injection of stain be of value, and there seems to be no way of bringing this about. The controlling of the pressure by which the dye is introduced is of no aid as no preoperative determination of the thickness and permeability of the walls of the tracts is possible.

2. From the study of the morphology of these tracts it is found that the majority are simple midline tubular structures. The great majority of specimens examined included large portions of normal tissue unnecessarily removed. No rule can be made as to the size of the dissection which will remove only pathologic tissue, but it is interesting to note that for midline tracts a block not exceeding 2 cm. in width would have been sufficient. The length as determined by the number of openings would have been adequate had the dissections started at a point 1 cm. below the lower opening and extended to a point 5 cm. above single openings and not over 1 cm. above the uppermost of multiple openings. The one specimen which had a tract reaching 7 cm. above a single opening was easily recognized clinically. When lateral openings were present, incisions not more than 0.5 cm. outside them

would have removed all diseased tissue. The one tract which extended obliquely from a single central opening might have been partially retained had the block been only 2 cm. in width.

None of the tracts in this series extended beneath the coccygeal fascia, but it is realized that the occurrence of some structures which have communicated with the neural canal have been reported.<sup>4</sup> These were situated over the sacrum or low lumbar region, higher than the usual site of a pilonidal sinus. Because of this the identification of such structures with the ordinary pilonidal sinus may be disputed.

3. Infection plays an important part in all these specimens. There is evidence of its presence even beneath the simple dimples. It seems probable that the lateral extensions are all formed by infection which is blocked from its natural escape and burrows along the lines of least resistance. The accessory openings, by appearance as well as by their clinical history, have been formed by the rupture of infected tissue from below. The persistent granulating inflammatory sinus becomes epitheliated perhaps from both ends. (The histologic picture of these extensions differs in no way from that of the epitheliated sinus tracts present in other chronic infections, such as osteomyelitis.) In a recently formed sinus or in one which was recently the site of a destructive inflammatory process no epithelial lining is found.

In general, it is probable that before any abscess forms the pilonidal sinus is a simple tract with never more than one or two closely associated sinus openings.

4. The study of the specimens from the secondary resections suggests that the recurrence or persistence of symptoms is probably due to the retention of infected tissue or to faulty healing which causes the formation of an infected dead space. The impression that "recurrence" is always caused by the growth of the retained tract or its accompanying structures, the hair follicles and sebaceous glands, is not substantiated. We were unable to demonstrate that epithelial elements left behind at a previous excision undergo any changes except those incident to infection.

From this study it seems most logical to make the dissection as small as possible in order to insure good healing and to rely on the surgeon's ability to recognize diseased tissue in a field which is not obscured by excessive blood or by dyes.

#### SURGICAL APPLICATION

If our observations are correct, we may consider that we are dealing with a simple, rather circumscribed, structure. Persistence of a draining

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4. Ripley, W., and Thompson, D. C.: Pilonidal Sinus as the Route of Infection in a Case of Staphylococcus Meningitis, *Am. J. Dis. Child.* **36**:785 (Oct.) 1928. Moise, T. S.: *Surg., Gynec. & Obst.* **42**:394, 1926.

sinus after any method of treatment is due to the presence of chronic infection, in epithelial elements or in other tissue, either present from the start or developing subsequently but always in such a location as to prevent the sound healing of the wound.

Any attempt to conform to this concept and at the same time to reduce the economic loss to a reasonable minimum involves first of all getting away from the idea that cure depends on a successful radical excision. Cure does depend on the eventual removal of all diseased tissue, both that which is present at the time of operation and that which may appear in the wound during the process of healing. If this is true, it follows that the care of the wound is of at least equal importance with the operation itself.

In a bloodless field, where no dye is present to invade lymphatics or stain normal tissues, it is usually easy to recognize diseased tissue by its appearance and consistency. It is always easy to recognize it by its behavior in a healing wound. Thus the surest way of eliminating the epithelial elements and accompanying or subsequently developing inflammatory tissue would be by a series of minor surgical procedures extending over the entire time it takes for the wound to heal.

Such a program can be carried out only if the patient is ambulatory and unhospitalized. The method implies the use of local rather than general anesthesia, but the anesthetizing substances must be administered in such a way as to avoid the danger of disseminating infection. It also implies that the entire management of each case should be in the hands, or under the supervision, of the surgeon who undertakes to effect a cure.

#### TREATMENT OF AMBULATORY PATIENTS BY EXCISION WITH THE CAUTERY

A method of treatment in accord with our present concept of the disease is now being used at the Massachusetts General Hospital and was described in 1932 by F. D. Stanton of the Dover Street Clinic.<sup>5</sup> The operation is performed under local infiltration anesthesia, but only the skin along the midline is anesthetized so that there is no disseminating of infection into sound tissues (fig. 10). The cutting is done entirely with a cautery knife;<sup>6</sup> this method provides a bloodless field which facilitates the recognition of unstained diseased tissue, not only by its appearance but by the fact that such tissue is less readily divided by the cautery knife than is normal fat. The diseased tissue is first completely divided longitudinally down to the sacrococcygeal fascia and is then removed in halves by slightly undercutting the edges of the skin (fig. 11). The resultant narrow cavity is packed, and the

5. Stanton, F. D.: *Tr. Am. Coll. Proct.* 9:69, 1932.

6. A Post cautery point no. A 4 at maximum heat is used.

patient is allowed to go home. This procedure has proved to be a minor operation producing no systemic reaction. Not only is hospitalization avoided, but the patient remains ambulatory throughout, and the total time lost from work may be as little as half a day.

At first glance it appears that dead space must result from the failure to remove any skin. This would undoubtedly be the case were it not for the careful application of postoperative dressings which rivals in importance the operation itself. Each time the wound is dressed the floor of the cavity is scrutinized, and any unhealthy-looking area of

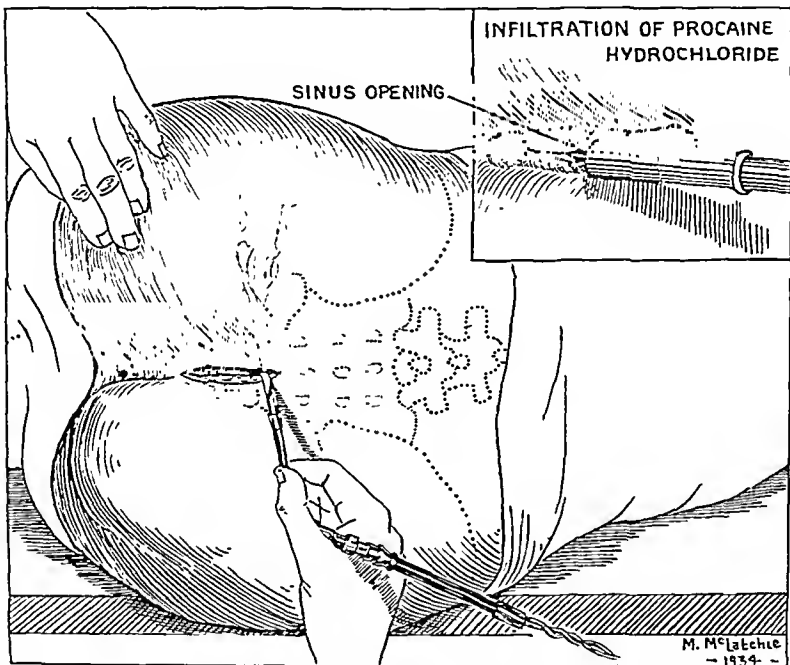


Fig. 10.—Cautery excision of a pilonidal sinus. The left buttock is retracted by an assistant. The cutaneous incision must be made rapidly to avoid charring.

granulation tissue is painlessly curetted down to a solid base or excised with the cauterization knife. By this method of fractional operation whatever diseased tissue may have been overlooked at operation is recognized and removed during the period of healing. The cavity is kept packed until it has been obliterated by the growth of healthy, solid granulation tissue, which then appears as a narrow coxcomb between the two edges of skin. It is important to keep this coxcomb down to the level of the surrounding skin until the whole surface has become epithelialized. The end-result is a linear midline scar.

Sometimes the last inch shows a disinclination to heal or heals and splits repeatedly before becoming completely epithelialized. This may be corrected by making an incision through the normal skin parallel to and 2 cm. away from the offending area, thus relieving the lateral tension on the scar. Both wounds will then heal rapidly and satisfactorily.

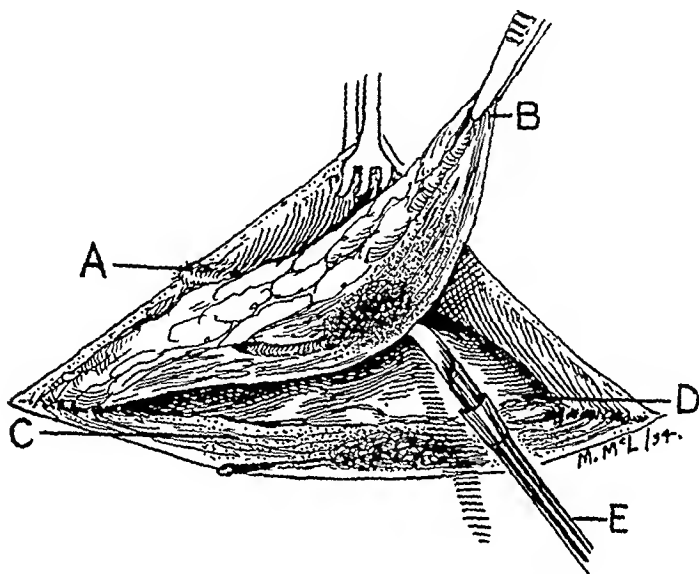


Fig. 11.—The specimen is removed in halves. Bleeders are stopped immediately by a touch of the cautery point. The fascia is sensitive and if approached too closely requires infiltration of procaine hydrochloride. This sketch shows the skin undercut farther than is usually necessary to get around the diseased tissue. *A* shows the sinus; *B*, the left half of the specimen being removed; *C*, the right half of the specimen before removal; *D*, the sacrococcygeal fascia; *E*, the cautery knife.

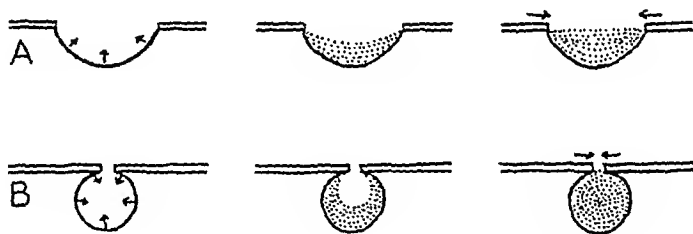


Fig. 12.—*A* is a cavity formed by radical excision with a knife; *B*, cavity formed by conservative excision with the cautery. Cavity *B* fills more rapidly than does cavity *A* because it offers a more extensive base for the growth of granulation tissue.

The healing of the cavity left by conservative excision with the cautery is more rapid than that left by radical excision with a knife, partly because less tissue has been removed and partly because of the more favorable shape of the cavity (fig. 12). It is apparent from the diagram that *B* would fill in more rapidly than *A*, even were they of

the same capacity, owing to the more extensive base offered for the growth of granulation tissue.

The fact of the patient's being ambulatory introduces three theoretical difficulties, all of which are in practice easily controlled: 1. Postoperative oozing may be effectively prevented by moistening the original gauze pack with a hemostatic solution, such as thromboplastin. 2. Postoperative pain, though it is slight, may be still further reduced by applying to the edges of the incised skin one of the analgesic preparations such as butesin. 3. Saprophytic infection, so commonly seen in the large granulating wounds resulting from radical excision, may be minimized by keeping the gauze packing saturated with a nonirritant antiseptic solution, such as metapen or mercurochrome.

After the first return visit on the third or fourth day it may not be necessary to treat the wound oftener than once in four or five days, but the patient must be convinced that these dressings are a more important part of the treatment than the operation itself.

The dressings are best carried out, as is the operation, with the patient lying on his right side with the knees drawn up, the left buttock retracted by an assistant and the operator sitting down with the necessary materials within reach (fig. 10). If the operation has been performed in the outpatient department, it follows that the postoperative management will be under the direct supervision of the original operator. We consider this essential to the complete success of the method.

We believe that by this method persistent draining sinuses can be entirely prevented and that once the wound is healed, true recurrence will never take place. A true recurrence is theoretically possible only by assuming that a retained epithelial element would not prevent the healing of the wound and that at a later date it would become infected and initiate a repetition of the original onset. Our observations lead us to believe that no such assumption can be made. Sufficient time has not yet elapsed, however, to enable us to say, on the basis of the lesions already treated by this method at the Massachusetts General Hospital, whether such an occurrence is a practical possibility or not.

#### THIRD SERIES: RESULTS OF CAUTERY EXCISION

Fifty cautery excisions have been performed during the past eight months at the Massachusetts General Hospital, approximately the same ratio of secondary recurrent cases and new cases prevailing as in the former series. Twenty-nine of the fifty wounds are known to be completely and satisfactorily healed. In the remaining cases either the wounds are too recent to be healed or the patients have returned to their local physicians for dressings so that we do not know the present status of the wound. There are no known failures or recurrences as yet.

There were several instances of delayed healing about which more will be said presently. Of the twenty-nine healed wounds, twenty-four healed in an average period of nine weeks; the shortest period of healing was between five and six weeks. The general average for the time of healing is raised to two and seven-tenths months, however, by five cases of delayed healing (table 4).

The average postoperative stay in the hospital was less than one day. Sixteen patients were operated on in the outpatient department, and of the thirty-four who were operated on in the hospital, almost all went home on the same or on the following day. The majority of these thirty-four patients were admitted to the hospital from habit, since up to eight months ago all the patients with pilonidal sinus had been hospitalized. Seven operations, however, were performed in the hospital advisedly, since the extensive scarring present offered too great an obstacle to the successful use of local anesthesia. General anesthesia was therefore used in seven instances. In the other forty-three cases local anesthesia proved perfectly satisfactory.

TABLE 4.—*Results of Caustery Excision in the Third Series (Fifty Cases)*

Gross rate of recurrence.....	0 (to date)
Average postoperative hospitalization.....	1 day or less
Average time lost from work.....	1 week
Average time to heal (29 cases).....	2.7 months

The loss of time from work varied from none up to two weeks. The majority of patients stated that the maximum discomfort occurred during the third or fourth postoperative day, but in no case was it sufficient to prevent a visit to the outpatient department. It was not unusual for the patient to attend a ball-game or a dance on the day of operation. There has been no instance of acute infection following operation, in spite of the fact that one excision was performed in the presence of an acute abscess.

Several of the practical points gained through our experience with the caustery method may be worth mentioning without comment. In dividing tissue with the caustery, ease of cutting is directly proportional to the tension exerted on the tissue. Pressure on the caustery blade should never be necessary. One excision was performed with the electrosurgical diathermy unit, but hemostasis was much inferior to that produced by the caustery. Bleeders should be controlled as soon as encountered to ensure a really bloodless field. The cutting should be deliberate to get the best hemostatic effect, except during the maneuver of undercutting the edges of the skin, which must be rapidly done to avoid a slough. The natural tendency to follow along the surface of the coccyx down to its tip must be resisted, except when the presence

of diseased tissue makes it necessary, as the resultant deep hole is slow to heal. An incision connecting the posterior portion of the perineum with the gluteal cleft greatly complicates healing and usually results in an irregular scar. For this reason a two-stage procedure should be considered in cases of extensive involvement with openings near the anus and over the sacrum. The excision of an acute abscess is unsatisfactory because of hyperemia and friability of the tissues. The result in our one case, however, was good.

As for the postoperative care, it may be considered to fall into two stages, divided by the disappearance of all slough from the wound. During the period of slough dressings may need to be changed every two days to prevent odor. Any attempt to remove the original packing before the fourth postoperative day, however, causes pain and bleeding and should not be made. Until all slough has disappeared there is no object in looking for areas of defective healing, as they show up only in contrast to clean, healthy granulation tissue. Undercut edges of skin if allowed to stick down will delay healing and form a poor scar.

Once the slough has separated, the wound should fill rapidly with healthy granulation tissue and close to a narrow linear scar, the total time from the operation to the formation of the scar being six weeks or less. As already intimated, in several of our cases healing was delayed far beyond this schedule. This might be anticipated in the case of unusually large or ill cared for wounds. The puzzling thing is that some of the wounds which apparently had everything in their favor took the longest time to heal. The delay was not due to defective healing in definite circumscribed areas of the wound, since such areas were always removed on sight, but the whole wound, after progressing to a certain point, seemed to have lost all stimulus to further healing, so that weeks passed with no appreciable progress being made beyond that point. Coincident with this abrupt cessation of healing there was usually extreme sensitiveness in a wound which had not exhibited that symptom before. Often, but not always, the granulation tissue appeared pale and smooth when before it had been red and granular. Sometimes there was actual regression, as if the tissue had been destroyed by a cytolytic ferment.

#### DELAYED HEALING

It is our purpose here not to write a monograph on the factors influencing healing in a granulating wound but only to suggest the need for such a monograph. Several hypotheses are suggested by analogous phenomena observed elsewhere. In phagedenic ulcers, for example, actual destruction of tissue is brought about by toxins or ferments formed by the symbiotic organisms in the wound. This



action can often be stopped by the oxygen liberated from such a substance as zinc peroxide, because it kills the bacteria, restores the vitality of the tissue cells or does both. It is possible that the delayed healing of certain pilonidal sinus wounds is due partly to bacterial action and partly to reduction of blood supply by contraction of the original deep layers of granulation tissue as their fibroblasts mature to connective tissue cells. It is certain that all these wounds are constantly contaminated from their proximity to the anus, so that such a hypothesis is not at all far-fetched. At present we are experimenting with various bactericidal and oxygenating substances in an attempt to shorten the period of healing and discover and avoid whatever mechanism is responsible for these peculiar cases of delayed healing.

In conclusion, we believe the successful treatment of pilonidal sinus to be primarily a problem of wound healing, the exact method by which the abnormal tissue is recognized and removed or destroyed being of slight relative importance. While the method described is an improvement over older methods, particularly in respect to lessening economic loss and recurrence of symptoms, there is still room for great improvement through a better understanding of the factors influencing the healing of granulating wounds.

#### SUMMARY AND CONCLUSIONS

The results of treatment in a series of one hundred and eighty-one cases of pilonidal sinus have been analyzed.

A study of the pathologic changes in forty-four surgical specimens of pilonidal sinus has been made.

The economic loss incident to any method of treatment based on radical excision, even under ideal conditions, is greater than the importance of the disease warrants.

On morphologic grounds there are no indications for radical excision.

In a bloodless field unstained by dye diseased tissue is recognizable by its appearance and consistency.

During wound healing diseased tissue is distinguishable from healthy tissue by its lack of normal growth.

A method of treatment by repeated excisions with the cautery of diseased tissue only, carried out as minor operations on ambulatory patients, is described and recommended.

A preliminary report on the treatment of fifty lesions by excision with the cautery is made.

# PATHOLOGIC CHANGES OF DISEASED GALLBLADDERS

## A NEW CLASSIFICATION

EDMUND ANDREWS, M.D.

CHICAGO

Very early in our studies on the gallbladder it became clear to my associates and me that the present systems of classification of cholecystitis were at fault. As the work progressed it became with increasing frequency impossible to correlate the pathologic changes with either the clinical, bacteriologic or the postoperative course. As increasing numbers of cases became available for study, these discordances were so glaringly evident that it was clear that our methods of pathologic classification were inadequate (figs. 1 and 2). For these reasons the various conditions were entirely reclassified *de novo*, as will be elucidated in the comment.

## MATERIAL AND METHOD

The material studied consisted of a series of fifty-four specimens which were removed at operation in cases in which elaborate chemical and pathologic studies as well as chemical studies had been made, as reported in a recent paper.<sup>1</sup> In sixty-one other cases, chemical, bacteriologic and clinical studies were made, but no sections cut at intervals of 2 cm. were studied. In many cases a technic of excision was carried out in which the gallbladder underwent a minimum operative manipulation. A clamp was placed on the fundus, and whenever possible, by making traction on the gallbladder itself, the cystic duct was exposed without handling the main body of the viscus. The duct was clamped, and the gallbladder was removed in a retrograde manner, being touched only by the clamp at each end. Of course this ideal was not always achieved, but practice enabled us to carry it out in a sufficient number of cases to warrant drawing very definite conclusions as to how much of the previously reported pathologic change in the gallbladder was really due to mechanical injury.

Cultures were made of both the bile and the wall of the gallbladder, and the gallbladder was then emptied and the interior inspected, following which a solution of formaldehyde was injected into it so that it was distended. After a certain amount of hardening had taken place the gallbladder was immersed in a solution of formaldehyde for complete fixation. The specimen was then divided into a series of rings about 2 cm. wide. These rings were embedded in paraffin (the larger ones in pyroxylin) and sections were cut and stained with hematoxylin and eosin. A study of these serial sections was made, the pathologic changes encountered in each of the various layers of the wall being noted on a special form, and the changes, together with the clinical and bacteriologic data, were recorded in the tables.

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From the Department of Surgery, the University of Chicago.

1. Andrews, E.: Detailed Studies of a Series of Gall-Bladder Cases, Surg., Gynec. & Obst. 57:36, 1933.

In view of the previously mentioned failure to correlate the clinical signs and the pathologic changes, a grouping was made on a very broad basis; i. e., one group contained gallbladders showing signs of clinical activity, either active or very recent, and the other group contained those that were removed between attacks when the patients were not acutely ill. A small group of gallbladders which proved to be normal, removed for various reasons, was included in a third group.

It will be seen from examination of table 1 that we have been rather radical in attacking the recently inflamed gallbladder. In only one case of the entire series was operation performed because of fear

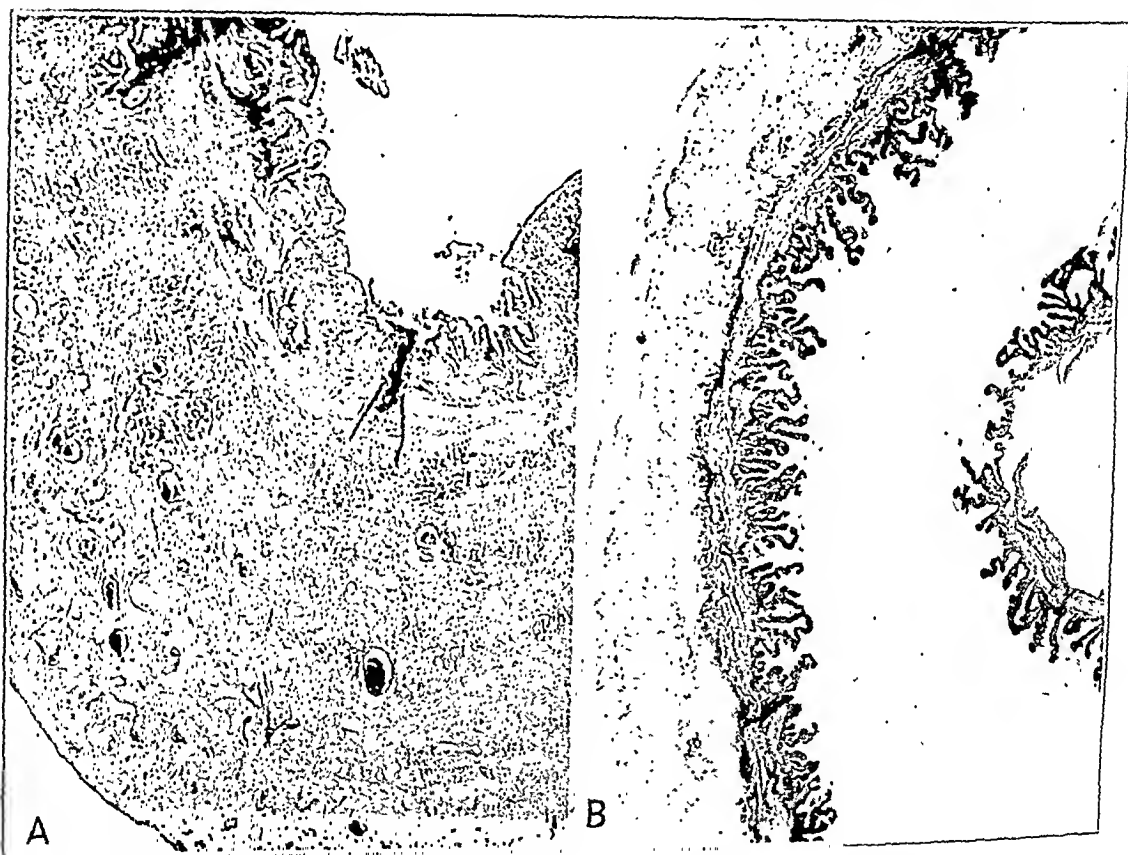


Fig. 1.—Photomicrographs illustrate the lack of correlation between the clinical signs and the histologic picture in cases of disease of the gallbladder. *A* is a section from the gallbladder of a 34 year old woman who presented no symptoms at the time of operation or for two weeks before. She previously had had many severe attacks of colic. The last attack was afebrile, and the white blood count did not exceed 8,000. A stone was found in the cystic duct. Grossly, the gallbladder was markedly thickened and hard to the touch. Histologically, a very severe degree of cholecystitis was present. Reduced from a magnification  $\times 23$ . *B* is a section from the gallbladder of a patient who had many severe attacks of colic for twenty years. They occurred almost daily for one month. Slight jaundice was present in the last attack nine days before operation. The area was still very tender at the time of operation. The patient was cured by cholecystectomy, according to follow-up reports. Grossly, the gallbladder was normal, and histologic examination also showed a practically normal gallbladder.

of rupture. All the other gallbladders were deliberately excised rather promptly after the subsidence of the acute attack. This had been justified in our own experience by various findings, which will be discussed later, and also by the recent occurrence in the literature of a considerable group of papers calling attention to the fact that it was safe to operate on many acutely inflamed gallbladders.<sup>2</sup> Our own operative experience has amply confirmed this. There were no deaths in the group of acute cases of disease of the gallbladder, and the postoperative morbidity was but slightly greater than in the group of chronic cases. In fact, it is quite curious that the worst postoperative results and the only postoperative death were in the group in which the gallbladders were normal. While it must be freely confessed that the technical difficulties of surgical intervention in cases of recent attacks are considerably greater, it appears from our operative results that the difficulties are harder only for the surgeon and not for the patient. Most striking of all is the fact, which can be elicited from a study of tables 1 and 2, that the microscopic appearance in the so-called cases of acute or recent disease of the gallbladder showed little more extensive pathologic change than in the group in which operation was performed during quiescent intervals.

#### BACTERIOLOGIC OBSERVATIONS

Most of the previous studies on the bacteriology of cholecystitis were made by technics which today do not seem adequate. Recent demonstrations of the rich bacterial flora of the normal liver<sup>3</sup> and gallbladder<sup>1</sup> make it quite clear that to be of any real significance the studies must not simply demonstrate the presence or absence of bacteria but must be quantitative. Since it has been shown that many pathogenic bacteria are normally present, in order for the result to be of clinical importance an increase in the normal flora must be demonstrated. On the other hand, simple swabs may often lead to negative results in cases in which culture of a larger amount of tissue or bile shows many microorganisms.

These bacteriologic studies are being reported in full in another paper,<sup>4</sup> but on account of their relation to the pathologic and clinical

2. Miller, R. H.: Acute Cholecystitis, *Ann. Surg.* **92**:644, 1930. Judd, E. S., and Phillips, J. R.: Acute Cholecystic Disease, *ibid.* **98**:771, 1933. Lahey, F. H.: Acute and Subacute Cholecystitis, *S. Clin. North America* **13**:595, 1933. Stone, H. B., and Owings, J. C.: The Acute Gall-Bladder as a Surgical Emergency, *Ann. Surg.* **98**:760, 1933.

3. Ellis, J. C., and Dragstedt, L. R.: Liver Autolysis in Vivo, *Arch. Surg.* **20**:8 (Jan.) 1930. Andrews, E., and Hrdina, L.: Cause of Death in Liver Autolysis, *Surg., Gynec. & Obst.* **52**:61, 1931. Andrews, E.; Rewbridge, A. G., and Hrdina, L.: Causation of B. Welchii Infections in Dogs by Injection of Sterile Liver Extracts or Bile Salts, *ibid.* **53**:176, 1931.

4. Andrews, E., and Henry, L. D.: The Bacteriology of Normal and Diseased Gall-Bladder, *Ann. Surg.*, to be published.

TABLE 1.—*Tabulation of Detailed Findings*

Name	History	Last Attack, Time Before Operation	Roentgen Examination	Gross Appearance of Gallbladder	Stones	White Blood Cells in Bile	Cultures		Postoperative Course	Microscopic picture		Mucosa		
							Wall of Gallbladder	Bile		Asymmetry	Rokitansky-Aschoff Sinuses	Ulcer	Cellular Infiltration	Polymorphonuclears
Church	Nausea; vomiting; jaundice	1 day†	N.V.	Thick; mild acute infection	Yes	0	S.	S.	Stormy, subdiaphragmatic abscess	No	None		Cholesterosis	
Deutsch	Many attacks of colic	2 days	N.V.	Not thick; hour-glass adhesions	Yes	.....	S.	S.	Smooth	No	None		Cholesterosis	
Essig	Severe attacks for 15 months; fever	5 days	N.V.	Normal	Yes, in common duct	1,260	Strep. viridans		Rather stormy	No	None		Cholesterosis	
Fassal	Deep painless jaundice and acute attacks of colic	Recent	Not made	Dilated; normal	No	.....	0	B. welchii; B. coli	.....	...	...	...	...	...
Gilmore	Dyspepsia; many attacks of biliary colic for 3 years	6 days	N.V.	Large; thick	Yes	2,500	B. coli	B. coli	Uneventful	No	None	...	...	...
Lathrop	Typical attacks of colic for 7 mos.; some with jaundice	5 days	N.V.	Small; thick	Yes, paste	.....	Bacteria	S.	Uneventful					
Nelson	Many acute attacks	9 days	N.V.	Very thick; tense	Yes	.....	S.	S.	Uneventful	No	None	3+	4+	2+
Rudley	Many attacks of colic; jaundice lately	Few days	Slight	Tense	Yes	750	Strep.	Strep.	Uneventful	Yes	None	...	...	...
Springer	Many typical attacks of colic	Few days	Not done	Large	Yes	.....	Staph.; B. welchii	Staph.; B. welchii	Smooth	All layers blended.			Extreme	
Vazquez	Repeated attacks of colic; chills and fever; belching of gas	5 days	N.V.	Thick sub-acute inflammation	Yes	2,400	B. welchii; B. coli	B. welchii; B. coli	Fever	...	...	...	...	...
Bache	Several attacks of biliary colic, last with jaundice	5 days	N.V.	Small; thick	Yes	.....	Staph.	Staph.	Not smooth	Yes	1+	...	...	...
Baumgartner	Three attacks of biliary colic in last year; no jaundice	Recent	N.V.	Thick; white; packed with stones	Yes	3,124	Staph.	S.	Uneventful	...	...	0	0	...
Burke	Numerous attacks of biliary colic for 4 years	5 days	V.	Few adhesions, not very thick	Yes	4,262	B. diphtheriae	S.	Uneventful	...	...	...	...	...
Campbell	Many attacks in 1 year; deep jaundice	4 days	V.	Enlarged; thick; white	Yes	550	Staph.	S.	Uneventful	...	...	...	...	...
Ceresa	Entered hospital during very acute attack	3 days	Not done	Very thick	Yes	6,800	B. coli	B. coli	Smooth	..	...	1+	1+	1+
Crabbe	Entered hospital in first acute attack	5 days	N.V.	Subacutely inflamed	Yes	1,150	B. typhosus	S.	Ileus	...	...	1+	...	...
Dobrolecki	One attack 1 year before; another attack of jaundice	2 days before	N.V.	Shrunken; thick	Yes	4,250	Staph. and B. diphtheriae; B. alkaligenes		Smooth	...	...	Sl.	...	...
Dorn	Many attacks of biliary colic for many years; dyspepsia	Recent	V.	Dense; adhesions to duodenum	Yes	1,250	S.	S.	Uneventful	...	Few	...	...	...
Drechsel	Many attacks for 12 years	Recent	Faint	Large; thick; injected	Yes	3,460	S.	S.	Uneventful	...	2+	...	...	...
Hatfield	Many acute mild attacks recently	Recent but mild	Faint	Thin; no inflammation	Yes	2,346	B. diphtheriae	..	Uneventful	...	1+	...	...	...
Jenkins	Entered hospital with acute abdominal condition; large liver; no jaundice	5 days	Not done	Very thick; tense	Yes	1,250	S.	S.	Uneventful	...	...	Fibrous, actually		
Kennedy	Many attacks in last 5 months	1 day	Not done	Tense; thick	Yes	4,400	S.	S.	Stormy	2+	2+	...	Sl.	...
Mathews	Typical attacks for 20 years; jaundice for 9 days	9 days	Not done	Distended; adhesions	No	2,132	Staph.	S.	Uneventful	...	...	...	...	...
Owen	Attacks of biliary colic for 10 years; getting worse	Recent	N.V.	Very thick; large	Yes	2,176	B. coli	B. coli	Uneventful	...	...	...	...	...
Patterson	Constant pain in right upper quadrant for 8 months	Recent	N.V.	Distended; thick	Yes	3,240	S.	S.	Uneventful	...	...	...	...	...
Woodward	Admitted to hospital in subacute attack of 12 days' duration	Active	Not done	Enormous; dilated	Yes	1,026	S.	Staph. albus	Uneventful	1+	4+	Distal portion 4+ Proximal portion 3+	...	...

\* In this and in the other tables, N.V. means not visualized; V, visualized; S., under cultures, sterile; Sl., slight; D., diffuse; Pv., perivascular, and F., focal. The degree of infiltration is graded 1, 2, 3 or 4 plus.

† This patient also had an attack four years before operation.

Submucosa									Muscularis						Serosa															
Eosinophils	Distribution	Follicles	Edema	Fibrosis	Cellular Infiltration	Polymorpho-nucleats	Lymphocytes	Eosinophils	Distribution	Hypertrophy	Edema	Fibrosis	Cellular Infiltration	Polymorpho-nucleats	Lymphocytes	Eosinophils	Distribution	Edema	Fibrosis	Thickening	Cellular Infiltration	Polymorpho-nucleats	Lymphocytes	Eosinophils	Distribution	Comment				
...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	Few	...	...	2+	1+	2+	1+	...	1+	...	D. and F.	...	Accessory duct ?			
...	...	...	...	...	...	...	...	...	...	...	1+	...	...	...	...	1+	...	1+	1+	...	...	...	...	1+	D.	...	Histologically normal gallbladder			
...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	Had cancer of pancreas			
...	...	...	...	...	...	...	...	...	...	2+	4+	...	1+	...	1+	...	D.	4+	...	...	...	...	...	...	...	...	Dehydrated edematous gallbladder			
...	...	Sections near cystic duct normal; near wall of fundus resembles abscess cavity																...	...	...	...	...	...	...	...	...	...	...	...	...
...	...	...	...	...	...	...	...	...	...	2+	...	...	Sl.	...	1+	...	D.	...	...	...	...	...	...	...	...	...	Normal gall-bladder			
fibrosis.	...	Focal and perivascular infiltration by lymphocytes									...	4+	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...			
...	...	...	...	...	...	...	...	...	...	...	...	...	1+	...	1+	...	D.	1+	...	...	2+	...	1+	1+	D.	Slightly inflamed				
...	...	1+	1+	1+	1+	...	1+	1+	D.	1+	...	...	Sl.	...	1+	...	D.	4+	2+	3+	1+	Few	Few	3+	D. and F.	...	Cholangitis in liver			
...	...	...	...	3+	1+	1+	...	...	...	...	...	2+	3+	3+	Few	Few	D.	1+	1+	3+	1+	1+	...	...	D.	...	Prolonged low grade infection			
...	...	...	...	...	...	...	...	...	...	1+	...	...	1+	...	1+	...	D.	1+	...	1+	...	...	1+	1+	D. and F.	...	...			
...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	Normal microscope picture			
1+	D.	2+	0	0	2+	2+	2+	1+	D.	...	...	...	2+	1+	2+	1+	D.	1+	...	1+	1+	1+	1+	1+	D.	...	...			
...	...	1+	...	2+	1+	...	1+	...	D.	1+	...	2+	...	...	1+	...	...	...	...	...	...	...	...	...	...	...	Only one section studied; calcification in wall			
...	...	...	...	...	Sl.	1+	1+	1+	D.	2+	2+	1+	2+	2+	2+	2+	D.	4+	...	4+	Sl.	Few	Few	Few	D.	...	Histologic picture of early subsiding acute infection			
...	...	...	...	...	...	...	...	...	...	Sl.	...	...	Sl.	...	2+	1+	Pv.	...	...	...	...	...	...	...	...	...	Mechanical attacks			
...	...	...	...	...	...	...	...	...	...	2+	2+	...	Sl.	...	1+	Few	F. and Pv. D.	...	...	...	...	...	...	...	...	...	Hypertension from mechanical attacks			
...	...	...	...	...	...	...	...	...	...	...	...	...	Sl.	...	1+	...	D.	1+	...	...	1+	...	1+	...	D.	...	...			
infected sac. Various layers not clearly seen																														
...	...	...	...	...	1+	1+	1+	3+	D.	...	...	1+	2+	1+	1+	3+	Pv. and F.	1+	1+	1+	3+	2+	2+	3+	D. and F.	...	...			
...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	Normal gall-bladder			
...	...	2+	...	1+	1+	...	1+	...	D.	1+	...	...	Sl.	...	...	...	...	...	...	...	1+	...	1+	...	...	...	...			
...	...	2+	...	...	3+	...	3+	...	D.	Nearly 1+ destroyed	1+	4+	2+	...	...	2+	D.	2+	2+	3+	4+	...	...	4+	...	Fibrous wall				
3+	D.	...	...	3+	4+	4+	...	...	D.	...	...	...	4+	4+	3+	3+	D.	...	3+	3+	4+	3+	2+	2+	D.	...	...			
...	...	...	...	...	...	...	...	...	...	2+	...	...	Sl.	1+	...	...	D.	2+	2+	2+	2+	...	2+	...	D.	...	...			

TABLE 2.—*Tabulation of Detailed Findings in*

Name	History	Last Attack, Time Before Operation	Roentgen Examination	Gross Appearance of Gallbladder	Stones	White Blood Cells in Bile	Cultures		Postoperative Course	Microscopic picture		Mucosa		
							Wall of Gallbladder	Bile		Asymmetry	Rokitansky-Aschoff Sinuses	Ulcer	Cellular Infiltration	Polymorphonuclears
Clark	Pain; vomiting; jaundice, 5 years	Old	N.V.	Edema; soft adhesions	Yes	.....	B. diphtheriae	..	Smooth	...	...	...	...	...
Cowbey	Many typical attacks of colic	Old	V.; many stones	Normal; adhesions	Yes	.....	Few strep.	S.	Smooth	...	...	...	...	...
Herbstshelmer	Many typical attacks of colic; no jaundice and fever	Old	N.V.	Large adhesions; thick	No	.....	Str. viridans	..	Uneventful	No	...	...	...	...
Kling	Sense of indigestion; no typical attacks	Old	V. with stone	Normal; adhesions	Yes	.....	B. welchii	B. welchii	Uneventful	...	...	...	...	...
Miller	Nausea; vomiting; not typical attack	Old	N.V.	Normal; adhesions	Yes	1,150	S.	S.	Uneventful	...	2+	...	...	...
Mueller	Many afebrile attacks of colic for 1½ years; food intolerance for 8 years	Old	..	Normal; distended	Yes	.....	S.	S.	Uneventful	...	...	...	...	...
Naso	Many acute attacks; ? ulcer	Old	N.V.	Normal; distended	Yes	.....	...	...	Temp. 101 F. one week	...	...	...	...	...
Palt	Many attacks of colic with chills and fever; jaundice	Old	N.V.	Much thickened; normal	Yes	.....	B. coli; B. welchii	B. coli	Uneventful	...	...	...	...	...
Poncello	Stormy febrile attacks of colic for 4 months	Old (2 wks.)	N.V.	Shrunk	Yes	.....	Not done		Uneventful	...	...	...	...	...
Robillard	Atypical attack of colic in right upper quadrant; no fever or jaundice	Old	?	Normal	No	640	Few staph; Strep.	S.	Uneventful	...	...	...	...	...
Russell	Many years indigestion; one attack of colic with jaundice 1 year before	Old	Faint	Thickened; not acutely inflamed	Yes	1,250	Staph.	Staph.	Uneventful	...	...	...	...	...
Russell	Few mild attacks of colic; no fever or jaundice	Old	Faint	Thickened ??	Yes	262	S.	S.	Uneventful	...	...	...	...	...
Sass	Acute afebrile attacks of colic, 2 or 3 a year for 20 years	Old	N.V.	Thickened	Yes	0	B. coli	B. coli	Uneventful	2+	...	...	2+	...
Stengle	Many typical attacks of colic; jaundice once	Old	N.V.	Large and thick	Yes	350	Staph. subtilis	S.	Uneventful	...	...	Marked cholesterols	...	...
Frey	Attacks of colic for 4 years; also pain from ulcer	Old	Faint	Not thickened	Yes	1,225	B. coli; staph.	B. coli; staph.	Uneventful	...	...	...	...	...
Frost	Several attacks with jaundice	Old	N.V.	Slightly thickened	Yes	.....	B. coli	B. coli	Some pain and fever	...	...	...	...	...
Johnson	Repeated attacks for 1 year; chills; jaundice	Old	V.	Slightly thickened	Yes	450	S.	S.	Uneventful	...	1+	...	...	...
Logelin	Occasional attacks in last 3 years; no jaundice	3 wks.	N.V.	Thin	Yes	.....	Str. viridans; staph.	Gram-negative rod	Uneventful	...	...	...	...	...
Marks	Atypical abdominal pains; one typical attack recently	Old	V.	Normal	Yes	2,460	Staph.; B. welchii	Staph.	Uneventful	...	1+	...	...	...
Prokop	Numerous atypical attacks	Old	Not done	.....	Yes	4,000	S.	S.	.....	...	...	Very thin gall-bladder wall	3+	3+
Thompson	Severe attacks for 3 years	2 wks.	N.V.	Marked adhesions and edema	Yes	.....	B. coli	B. coli	Uneventful	...	...	3+	3+	3+
Wood	3 attacks 12 years ago; recurrences in last 3 months	Weeks	Not done	Large, thick	Yes	875	Gram-negative rod	.....	Uneventful	...	1+	...	...	...

*"Chronic" or Old Inactive Cases of Cholecystitis*

Submucosa									Muscularis						Serosa				
Eosinophils	Distribution	Follicles	Edema	Fibrosis	Cellular Infiltration	Polymorpho-nuclears	Lymphocytes	Eosinophils	Distribution	Hypertrophy	Edema	Fibrosis	Cellular Infiltration	Polymorpho-nuclears	Lymphocytes	Eosinophils	Distribution	Comment	
..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	F. Lymph channels in serosa	
..	..	..	..	..	..	..	..	..	..	1+	..	1+	2+	..	3+	1+	D.	Pv. had many lymphocytes	
..	..	..	..	..	..	..	..	..	..	Sl.	..	..	1+	..	1+	..	R.V.	D. Fibrosis in and muscularis	
..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	Pv.	
..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	Normal gall-bladder	
..	..	..	..	..	..	..	..	..	..	..	..	..	Sl.	..	1+	..	F.	F. Had dilated duodenum on roentgen examination before observation	
..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	Normal gall-bladder	
..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	Normal gall-bladder; duodenal ulcer; tuberculous lymph gland near cystic duct	
..	..	..	..	..	..	..	..	..	..	..	..	..	..	1+	..	..	..	Dilated lymphatics and follicles in muscularis	
..	..	..	..	2+	3+	..	..	..	..	..	2+	4+	..	..	..	..	3+	Fibrosis at gallbladder; cholecystostomy 4 years before	
..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	Normal gall-bladder	
..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	Normal gall-bladder	
..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	Operated on because of roentgen evidence of stone	
2+	..	..	Blends with mucosa						..	..	1+	2+	..	..	3+	2+	..	F.	
..	..	..	..	2+	..	..	..	..	Atrophy	4+	..	..	..	..	4+	D.	4+	D.	
..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	Normal gall-bladder	
..	..	2+	..	..	1+	1+	1+	1+	D.	3+	..	..	1+	1+	1+	1+	D.	D.	
..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	Essentially normal	
..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	1+	Pv.	Stone occluded cystic duct	
..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	1+	Pv.		
3+	D.	..	..	..	1+	1+	1+	1+	D.	1+	2+	..	3+	2+	2+	2+	D.	Abscesses in serosa	
..	..	..	..	..	..	..	..	..	Atrophy	..	..	..	..	..	..	2+	1+	F. and Pv.	



pictures they must be reviewed here. Cultures were planned so as to attempt to grow both the aerobic and the anaerobic organisms. Furthermore, the fluid content of the gallbladder was plated, and the number of bacteria per cubic centimeter was determined. The results of these studies showed clearly that the number of bacteria in the bile or fluid contents of the gallbladder in practically all cases was very small. Various organisms were found, but their numbers were generally under 100 per cubic centimeter of bile, a finding hardly consistent with a theory that cholecystitis is an infection. It was, furthermore, very noticeable that the number of cases in which there were bacteria in the wall of the gallbladder considerably exceeded those in which there were bacteria in the bile, indicating that whatever infection was present had been derived from the adjacent organs or the blood and not from the bile. It was astonishing that the number of organisms found in the acutely inflamed gallbladders did not, as a rule, exceed those found in the quiescent cases. It was striking that cultures from three of the four most severely damaged gallbladders were sterile. Of the thirty-six cases in our series in which operation was done during an acute attack or immediately afterward (5 days), bacteria were found in the wall in 42 per cent and in the fluid contents in 42 per cent, while in only 6 per cent were there high colony counts. This contrasts but slightly with the series of quiescent cases, in which bacteria were found in the wall in 33 per cent and in the fluid contents in 25 per cent, with high colony counts in 8 per cent. These figures are in general accord with the many previously reported series of cultures reviewed by *Magner and Hutcheson*.<sup>5</sup> *Judd, Mentzer and Parkhill*<sup>6</sup> commented on the fact that cultures in many cases of acute cholecystitis are sterile. *Haase*<sup>7</sup> found them to be sterile in 36 per cent of all cases. *Seeber*<sup>8</sup> divided his cases into afebrile and febrile groups. Cultures were sterile in 50 per cent of the cases without fever and in 25 per cent with fever. From the foregoing data there is but one conclusion to be drawn, i. e., that in the average case of biliary colic infection plays but a minor rôle.

#### ASYMMETRY OF PATHOLOGIC PROCESS

Our experience has indicated that a single section of the wall of a gallbladder is of rather doubtful significance. When serial sections are

5. *Magner, W., and Hutcheson, J. M.*: Cholecystitis, *Canad. M. A. J.* **27**:469, 1932.

6. *Judd, E. S.; Mentzer, S. H., and Parkhill, E.*: Bacteriologic Study of Gall-Bladders Removed at Operation, *Am. J. M. Sc.* **173**:16, 1927.

7. *Haase, W.*: Untersuchungen operativ entfernter Gallenblasen auf ihren Keimgehalt, *Beitr. z. klin. Chir.* **152**:305, 1931.

8. *Seeber, F. L.*: Klinische und bakteriologische Untersuchungen bei Erkrankungen der Gallenwege, *Deutsches Arch. f. klin. Med.* **167**:186, 1930.

made, it at once becomes clear that asymmetry of two types is frequently encountered. First, there is a considerable tendency for the sections nearest the fundus to show the most advanced changes (fig. 2). Second, in several of our cases there was a high degree of patchiness of the infiltration. This fact has been commented on by Feinblatt<sup>9</sup> and by Denton.<sup>10</sup> The latter regarded it as evidence that the underlying cause of the lesion is a vascular damage and that it corresponds to areas in

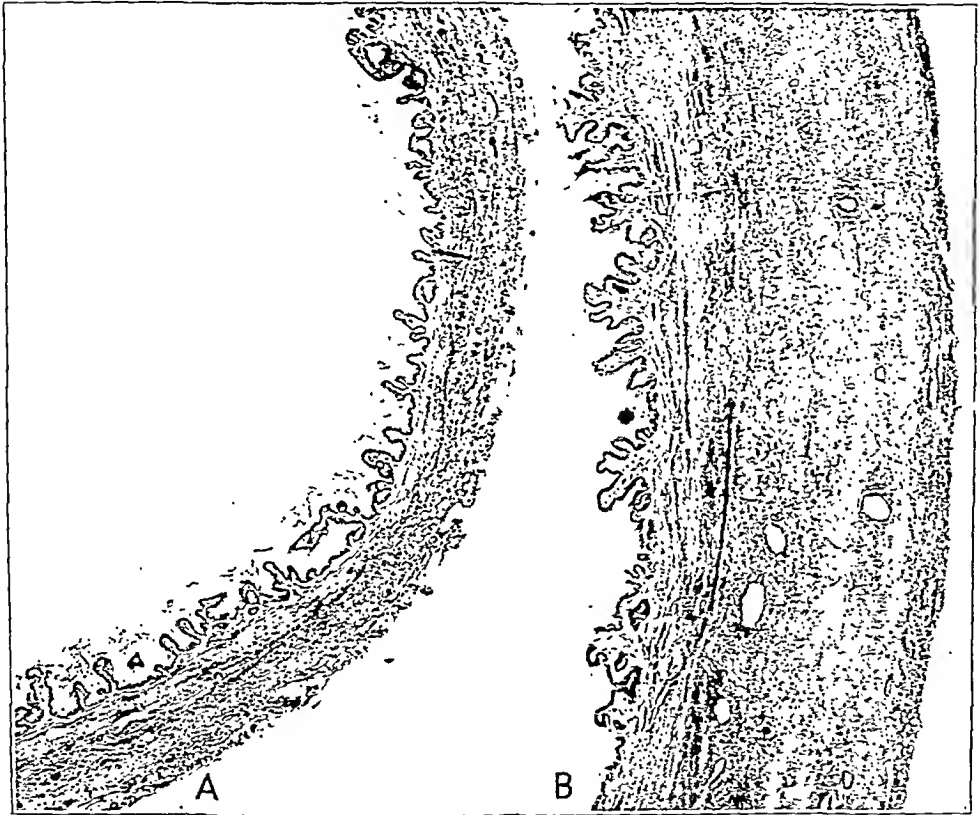


Fig. 2.—Photomicrographs showing different parts of the same gallbladder: *A*, a section near the duct of a practically normal gallbladder; *B*, a section near the fundus. Slight infiltration and marked edema and thickening of the serosa are seen. The picture is typical of cholecystitis of the moderate acute type.

which the blood supply is impaired. It was often much more marked on the hepatic surface of the gallbladder than on the free peritoneal edge.

9. Feinblatt, H. M.: The Infrequency of Primary Infection in Gall-Bladder Disease, *New England J. Med.* **190**:1073, 1928.

10. Denton, J.: The Mode of Origin of Gallbladder Disease, *Arch. Surg.* **14**:1 (Jan.) 1927.

This phenomenon has been discussed by one of us in a previous paper<sup>11</sup> and is believed to be an indication that infection, when it occurs, spreads by direct continuity from the liver, which it is known, has normally a rich bacterial flora.<sup>3</sup>

#### ROKITANSKY-ASCHOFF SINUSES

The Rokitansky-Aschoff sinuses were noted in a fairly high percentage of cases. However, in no case was it possible to trace any of the pathologic changes to them. They frequently passed through all the layers of the wall and had small dilatations on the peritoneal surface, and one wonders why they did not rupture under stress. Nevertheless, while focal infiltration of the wall of the gallbladder was common in our studies, there was not a single case in which these sinuses showed that they might be the foci of infection. This again is a strong argument against any theories of infection of the gallbladder of biliary origin.

#### ULCERS

Ulcers within the gallbladder are frequently mentioned in pathologic discussions, but in our experience they have been excessively rare, a true ulceration being present in only two of fifty-four cases. When the gallbladder is removed according to the technic described, without handling or squeezing or rubbing the wall against a gallstone, one does not find gaps in the mucosa. In almost every section of gallbladders removed without handling, the mucosa and its villi are absolutely intact and normal in appearance. Graham<sup>12</sup> called attention to the rapid autolysis of the mucosa of the gallbladder. It will, he said, entirely disappear in from five to six hours unless fixed. We have frequently noted the same fact in the gallbladder both of dogs and of human beings. There is also an intermediate stage in which the mucosa can be seen as a faint but distinct shadow in perfect outline, but which absolutely resists all staining. Care must be taken to differentiate this condition from necrosis of the inner coat. This leads one to suspect that many of the previously reported cases of ulceration of the wall of the gallbladder are due to artefacts of surgical trauma or to delay in fixation of the specimen.

#### THE THICKENED GALLBLADDER

Studies of the thickness of the wall of the gallbladder at first gave rise to very great confusion as the gross findings and the operative report often apparently disagreed with the microscopic data. A common incident was to find in the operative report that the surgeon had removed a large, white, thick-walled gallbladder and to find on preparation of the

11. Andrews, E., and Hrdina, L.: *Hepatogenous Cholecystitis*, Arch. Surg. 23:201 (Aug.) 1931.

12. Graham, E. A.: *Diseases of the Gallbladder and Bile Tracts*, Philadelphia, Lea & Febiger, 1928.

gross material in the pathologic laboratory that the wall was 10 mm. thick and that the viscus stood open of its own strength when empty. It was then very disconcerting to find on section that the wall was only slightly thickened and that it might appear practically normal. These experiences were so striking that we feared at first that the operative specimens were mislabeled. But subsequent study gave the correct answer to the problem. This is that in a general way most of the thickening of the wall of the gallbladder is edema. This was amply confirmed by our histologic studies. It is quite clear that the hardening and dehydration of a specimen would abolish much of this edema. The opposite occurrence was also not infrequent, that is, that an apparent thickening of the wall might take place during the process of fixation. This would probably depend on the degree of muscular contraction of the viscus at the time of its removal. A gallbladder which was distended might contract markedly either after or before fixation and appear thicker.

We believe that this factor of edema in disease of the gallbladder is the most characteristic feature of the pathologic picture. It takes place almost solely in the subserous layers, and it has proved striking that in our whole series the thickening of those gallbladders which were thicker than normal was due in at least 90 per cent of the cases to edema. Both Denton<sup>10</sup> and Feinblatt<sup>9</sup> commented on the importance of edema in the pathologic appearance of the gallbladder.

#### EMPHYEMA OF THE GALLBLADDER

In our experience empyema never occurs. It has been diagnosed repeatedly in the operating room when a creamy or milky content was found. However, in not a single case has the diagnosis stood up under chemical and microscopic examination. Invariably the milky fluid has proved to be either an emulsion of calcium carbonate or an emulsion of amorphous or crystalline cholesterol. It may be entirely dissolved by the addition of acid or by the addition of lipoid solvents. In a long series of counts of the white blood cells in the bile the surprising fact has come to the fore that not only are they not present in larger amount in acute cases but their numbers actually lessened during periods of activity of disease of the gallbladder. In many of the acute cases the cell content is markedly reduced. Feinblatt<sup>9</sup> emphasized this point. In the cases which he studied there were twenty in which the appearance was that of empyema. He said: "The great majority of direct smears failed to reveal frank pus; that is large numbers of polymorphonuclear cells with ingested bacteria. . . . In only 40 per cent of cases did the pus-like material give positive cultures." An especially illuminating case was observed at the University Clinics recently, in which a large abscess beside the gallbladder was evacuated, the con-

tents of which on microscopic examination showed practically no leukocytes. Denton,<sup>10</sup> who studied six hundred cases, arrived at the same conclusion. He said "Microscopic examination of the fluid in the gallbladder supported this view for it was ordinarily found that it contained very few cells of any description and was not pus," and "What is commonly referred to as empyema of the gallbladder would usually be described by some other term if the contents were examined microscopically."

TABLE 3.—*Tabulation of Detailed Findings in Cases in*

Name	History	Last Attack, Time Before Operation	Roentgen Examination	Gross Appearance of Gallbladder	Stones	White Blood Cells in Bile	Cultures		Postoperative Course	Microscopic picture		Mucosa		
							Wall of Gallbladder	Bile		Asymmetry	Rokitansky-Ashcroft Sinuses	Ulcer	Cellular Infiltration	Polymorphonuclears
Burge	.....	....	..	Normal gallbladder	....	.....	.....	.....	Died 2 days after operation					
Haggerson	Pain in right upper quadrant; atypical diarrhea	Old	V.	Normal; adhesions	Yes	873	S.	S.	Stormy; acute dilatation of stomach	No	None	Sl. cholesterosis		
Krader	No symptoms of gallbladder disease	....	V.	Normal	Yes	.....	S.	S.	Uneventful	No	2+	...	...	...
McLean	No symptoms of gallbladder disease; vague abdominal pain	....	V.	Normal	No	3,700	Staph.	S.	Uneventful	...	...	...	...	...
Pederson	Operation for abdominal ulcer; no attacks of colic	Ulcer pain is constant	Not done	Normal	Yes	.....	M. flavus	S.	Uneventful	Marked	....	...	...	...
Trilling	Duodenal ulcer	Old	Not done	Normal	Yes	.....	Staph.	S.	104 F. for 2 days	...	2+	...	...	...
Baum	Cholecystostomy 6 years ago; no typical history	None	V., with stones	Burled in dense adhesions	Yes	.....	B. Welchii	S.	Uneventful	...	2+	...	...	...

Of course, it is impossible to state that empyema of the gallbladder does not occur. We are simply recording the fact that in every case that we have observed in which the condition was thought to be empyema it has proved not to be.

#### CHOLESTEROSIS

Our own experience as well as theoretical considerations do not put great importance on cholesterosis. In the first place, it is found exactly as frequently in the normal as in the abnormal human gallbladder. No evidence has been produced which would indicate its association with cholesterol stones. Cholesterosis of the gallbladder is exceedingly common in several of the experimental animals, and in some of the herbivor-

ous animals it is so frequent that it is the rule and not the exception. In view of the fact that a cholesterol gallstone has never been reported as either occurring spontaneously or being produced in any animal experimentally, it seems rather far-fetched to associate cholesterosis with cholesterol gallstones in human beings. In our experience it has occurred no oftener in one type of gallbladder than another and no oftener with cholesterol stones than without them, and we believe that its occurrence may be ignored. Graham and Mackey,<sup>13</sup> who on the other

*Which Disease of the Gallbladder Was Clinically Questionable*

Submucosa																		Muscularis								Serosa								Comment
Eosinophils	Distribution	Follicles	Edema	Fibrosis	Cellular infiltration	Polymorpho-nucleus	Lymphocytes	Eosinophils	Distribution	Hypertrophy	Edema	Fibrosis	Cellular infiltration	Polymorpho-nucleus	Lymphocytes	Eosinophils	Distribution	Edema	Fibrosis	Thickening	Cellular infiltration	Polymorpho-nucleus	Lymphocytes	Eosinophils	Distribution									
...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	Normal gall-bladder							
...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	2+	...	1+	...	D. and F.	...	...							
...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	Normal gall-bladder							
...	...	...	Sl.	...	...	1+	1+	2+	D.	2+	...	...	3+	1+	1+	3+	D.	1+	...	...	Sl.	1+	...	1+	Pr.	Fundus and cystic duct normal; inflammation in medial portion								
...	...	...	...	...	...	...	...	...	...	...	1+	...	...	...	...	...	...	2+	Sl.	...	...	...	...	...	...	...	Had duodenal ulcer with stenosis							
...	...	...	...	...	...	...	...	...	...	Sl.	1+	...	1+	...	1+	...	F. and Pr.	1+	1+	1+	2+	...	1+	Few	F. and Pr.	...	...							

hand expressed the belief that it is of pathologic significance, reported it to be a common finding in otherwise normal gallbladders and stated, furthermore, that removal of the gallbladder for cholesterosis alone yields poor results. Aschoff,<sup>14</sup> Boyd,<sup>15</sup> Feinblatt<sup>9</sup> and many others have found it with special frequency in the normal viscus.

13. Graham, E. A., and Mackey, W. A.: Consideration of the Stoneless Gallbladder, *J. A. M. A.* **103**:1497 (Nov. 17) 1934.

14. Aschoff, L.: Lectures on Pathology, New York, Paul B. Hoeber, Inc., 1924.

15. Boyd, William: Surgical Pathology, ed. 3, Philadelphia, W. B. Saunders Company, 1933.

## CELLULAR INFILTRATION

If one compares the degree of inflammatory process in even an acutely infected gallbladder with that present in other viscera when acutely infected, one is at once impressed with the relative paucity of infiltrating cells. If, for example, a section of an infected urinary bladder or appendix is compared with one of the gallbladder, the fact is striking that the gallbladder, although it may be enlarged, thickened, dense or hard, has a relatively far smaller number of infiltrating leukocytes. The gallbladder, a section of which is shown in figure 3, was the fifth most severely involved in our entire collection, and it will be seen at once that it does not compare qualitatively with the inflamed urinary bladder or appendix. This is another clear indication of the fact that disease of the gallbladder in general is not simply an acute inflammation but a reaction of an entirely different sort.

Not only is the inflammation different in degree but in kind. The predominant cells in inflammation of the gallbladder in our series were not polymorphonuclear leukocytes. These do not occur regularly in the inflamed gallbladder in great numbers, and when they are present they generally are shadowed by the lymphocytes. The one clear feature was that the large number of eosinophils encountered in some cases was clearly associated with the subsidence of the disease, so that the eosinophilia of the gallbladder was an indication of progressive recovery. Of the infiltrating cells, the average of the whole series was at least ten to one round cells, there being more mononuclears than polymorphonuclears. Several cases were found, not only acute but quiescent ones, in which there was marked hypertrophy of all the lymphoid elements; the follicles in the submucous layers were hypertrophied, and the entire wall of the viscus was full of areas of dense focal infiltration of small lymphocytes. The occurrence of these in a normal gallbladder and the frequent finding in the dog of considerable lymphocytic infiltration of the wall of the gallbladder incline one to doubt if this represents an actual disease phenomena or is part of a general lymphatic hyperplasia (fig. 4). Marked hyperplasia of the submucosal lymph follicles is a common finding in appendixes that are not inflamed.

The type of infiltration that occurred was classified as focal, perivascular or diffuse, and when the entire series is summed up it is impossible to state what significance each variety has.

*The Mucosa.*—With but three exceptions in the acute series and one in the quiescent series the mucosa was normal, having no infiltration of wandering cells. In view of the many cases in which the mucosa appeared normal while the other layers showed marked evidence of reaction, one feels justified in arguing that whatever infection was involving the wall of the gallbladder it did not originate in the bile.

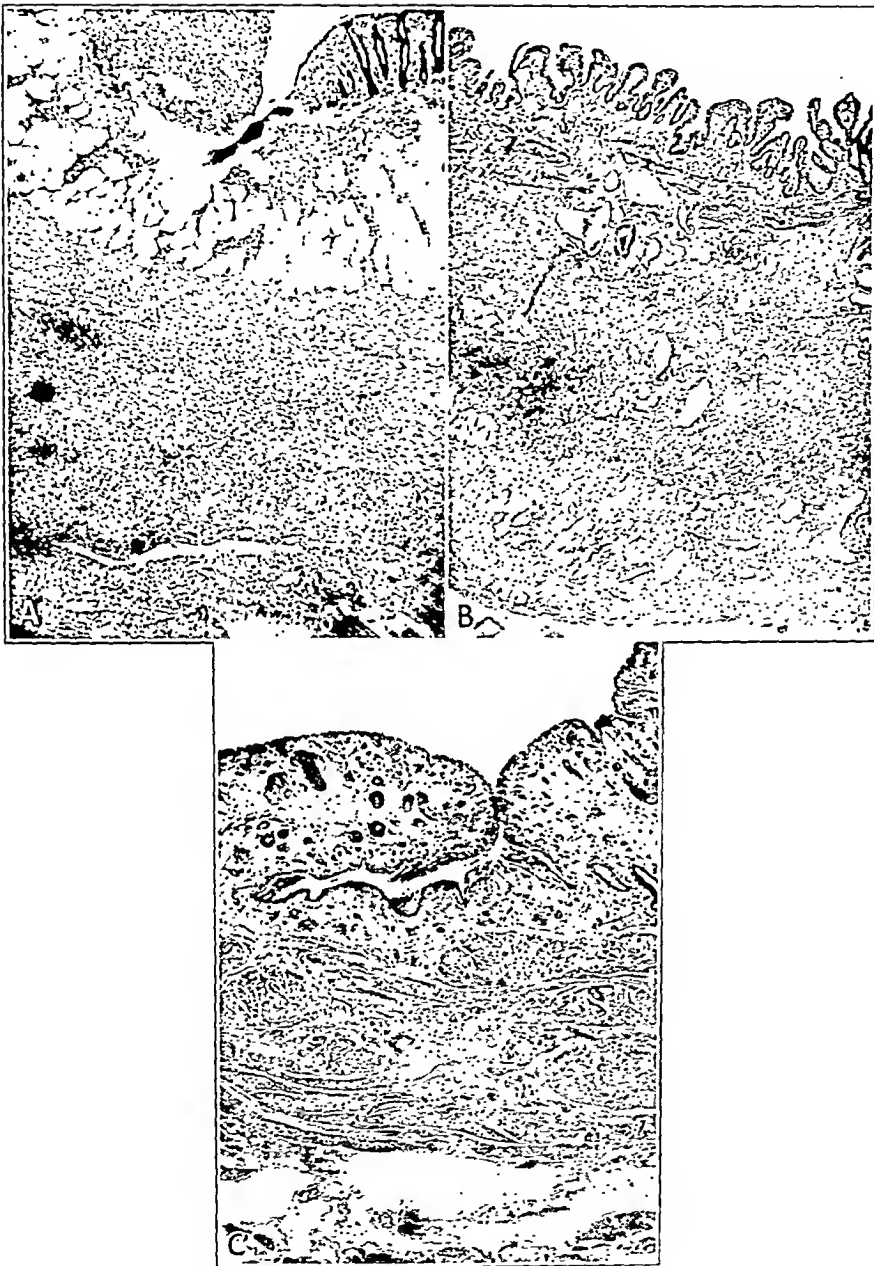


Fig. 3.—Photomicrographs for a comparison of acute infections of the gallbladder, appendix and urinary bladder. *A*, a section of the appendix, showing ulceration of the mucosa, extensive infiltration of the submucosa, muscularis and serosa with polymorphonuclear leukocytes and fibrinous exudate over the serosa. *B*, a section of the gallbladder with the mucosa intact and the submucosa normal. There is slight cellular infiltration of the muscularis (mostly round cells). Enormous edema and infiltration of the serosa produced marked thickening of the wall. *C*, a section of the urinary bladder showing enormous hyperemia and edema of mucosa, with moderate infiltration; moderate infiltration of the submucosa, and an essentially normal muscularis.



In studying the mucosa of a gallbladder several points must be kept in mind: First, there is the unusual tendency for the mucosa to undergo autolysis. Second, the damage from operative trauma on this very delicate membrane with long, thin villi is likely to be mistaken for pathologic change. We have attempted to avoid this when possible and thus to separate real changes from artefacts. Third, many writers have failed to recognize the fact that the normal mucosa of the gallbladder contains large numbers of cells which are quite similar to those which infiltrate the other coats in disease. Graham<sup>16</sup> said: "Normally, the mucosa contains *large numbers* of round cells (lymphocytes)." While he said that the mucosa is "relatively intact" and that most of the infiltration is in the deeper layers, Boyd<sup>15</sup> went considerably further. "It is



Fig. 4.—Photomicrograph of a section of a lymphoid gallbladder. The patient had had many attacks of colic, but none had occurred for many months. There were no signs of activity at the time of operation. There were stones in the bladder, but the ducts were free. Many enlarged lymph follicles are seen in the mucosa and the submucosa, and occasionally in the muscularis. Moderate focal infiltration of small lymphocytes is present in all layers. As far as we know, these follicles, which are often present, do not enlarge in real disease of the gallbladder. We are inclined not to regard such changes as signs of infection.

remarkable," he said, "how intact the mucosa may be in the worst looking gall-bladder." Our own experience agrees with Boyd's.

*The Submucosa.*—This layer enjoyed also the relative freedom from cellular infiltration that the mucosa did, although the normal lymphoid follicles varied considerably. In no case was either the mucosa or the submucosa infiltrated with cells when the outer layers were normal.

*The Muscularis.*—The muscularis and subserous layers were generally involved together with any pathologic process. Hypertrophy of

16. Graham,<sup>12</sup> p. 132.

the muscular wall did not appear to be associated with the presence of stones, nor did atrophy, which occasionally occurred. However, in the thickening of the wall, which occurred in many cases, the muscularis seldom takes an important part. Edema may take place with a slight spreading of the fibers, and a diffuse infiltration is common. However, although it may be thickened to double its normal extent in extreme cases, it never reaches proportions commonly found in the serosa.

*The Serosa.*—Edema, infiltration, hemorrhage, deposit of fibrin and especially dilatation of the lymphatics in the subserous layers account for practically all the thickening of the inflamed gallbladder. In every case it is the serosa which bears the brunt of the process, and its involvement is invariably greater than that of any of the other layers (fig. 5).

#### PATENCY OF THE CYSTIC DUCT

One of the most striking findings in our studies has been the definite correlation of the condition of the cystic duct with the pathologic changes in the gallbladder. This has been a far more accurate correlation than the presence of stone. With two or three exceptions gallstones were found in all our cases. But it was very striking that there was far less pathologic changes in the cases in which visualization under the x-ray indicated that the cystic duct was patent than in cases in which there was failure of visualization or in which operation revealed that the duct was closed. Examination of tables 2 and 3 reveal this fact sharply, and it is the one clinical correlation which has worked without exception.

#### FEVER

If the foregoing conception of cholecystitis is correct, it is difficult to account for the fever which often occurs, as fever is usually attributed to infection, which we do not believe to be a prominent feature. The evidence for this recently summed up is not only the failure of ourselves and practically all other observers to find bacteria in many cases of acute or chronic disease of the gallbladder (the cultures were sterile in an actual majority of even our acute cases) but the histologic studies of Feinblatt<sup>9</sup> and of Denton<sup>10</sup> as well as our own. Denton sectioned seventy acutely diseased gallbladders, and bacterial stains revealed organisms only in four.

A review was therefore made of the cases studied in which there was a temperature of over 100 F. while the patient was under observation or in which definite chills were reported. These manifestations seem to occur in only a minority of attacks. Many of the gallbladders which appeared the most diseased histologically had not caused fever in recent attacks while the patient was in the hospital. Closure of the

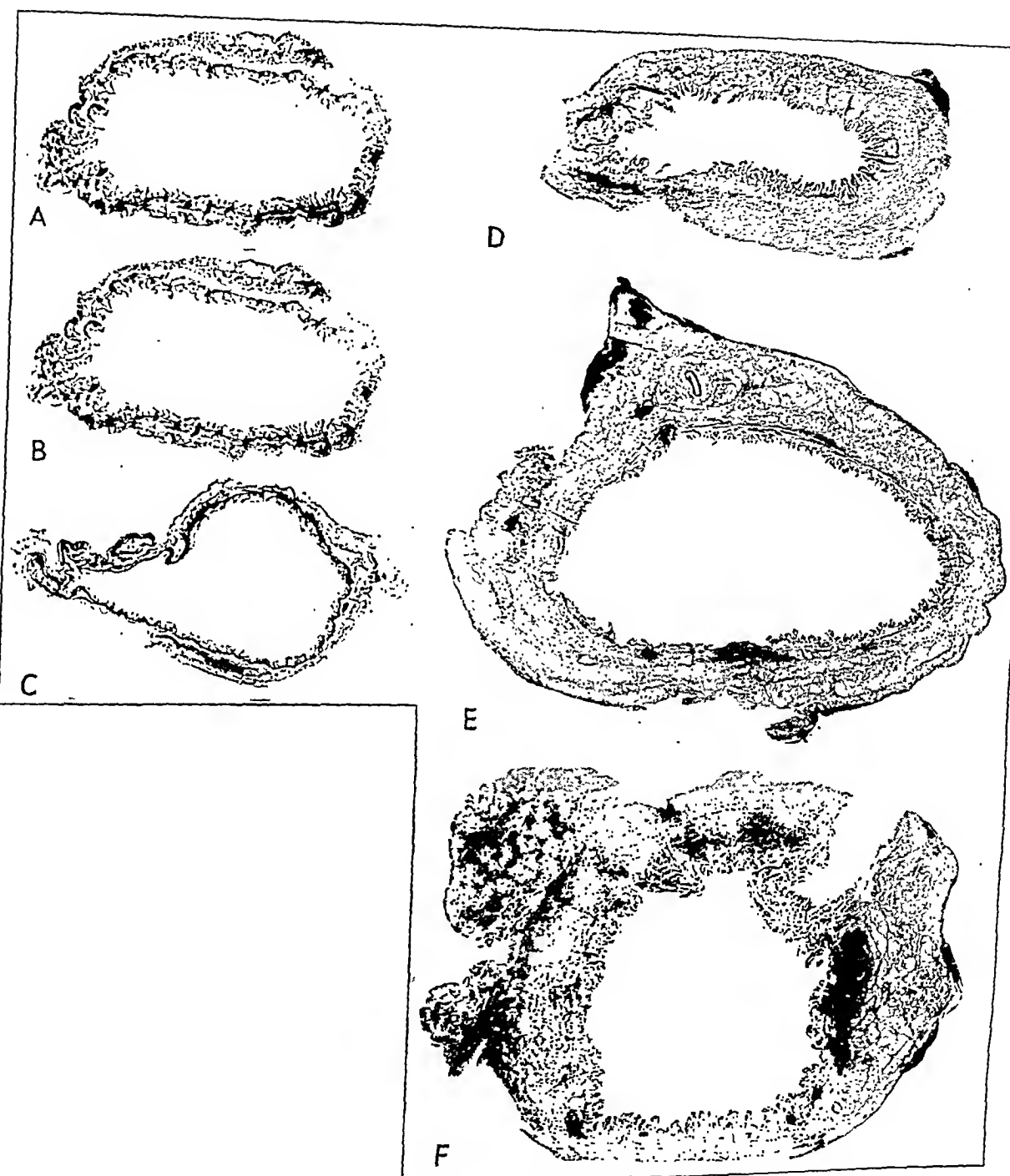


Fig. 5.—Sections through three different portions of a normal gallbladder (*A*, *B* and *C*) and of a thickened gallbladder (*C*, *D* and *E*). The measurements are as follows: *A*, *B* and *C*, the mucosa, 3 mm.; the muscularis, from 1 to 2 mm.; the serosa, from 2 to 5 mm.; *D*, *E* and *F*, the mucosa, from 3 to 5 mm.; the muscularis, from 2 to 3 mm., and the serosa, from 15 to 20 mm.

cystic duct alone did not appear to be in any way connected with the onset of fever, as it was often present both acutely and chronically without having produced fever. The one phenomenon that was definitely so connected was interference with the common duct. Twenty-eight patients were studied (the data on all are not included in the tables). Eleven had gross jaundice, and eight more, an elevation in the icteric index. One passed a single white stool on the second day of her attack; three on operation were found to have unsuspected calculi of the common duct, and four of the remaining five had massive inflammatory edema about the junction of the cystic and common ducts, in three cases accompanied by stones impacted in the cystic duct.

It is therefore clear that the age-old conception of "Charcot's intermittent fever" is not simply a manifestation of stone in the common duct. Obstruction of the common duct by inflammatory exudate about its junction with the cystic duct is probably relatively commoner than is indicated in the foregoing figures, because they were obtained by searching for records of obstruction of the common duct in our tables. It is well known that most cases of partial jaundice are to be explained on this basis. We believe that this is also the usual explanation of fever in cases of disease of the gallbladder.

#### COMMENT

No classification of diseases of the gallbladder can be of any use to clinicians that is not founded on sound ideas of the etiology, and especially of the relation of infection to cholelithiasis. It is only when modern knowledge of this subject is included that a reasonable classification can be arrived at, one which will not clash glaringly with the clinical and bacteriologic pictures as the present ones do. Many of the older classifications were based on ideas that have of necessity been abandoned. These include the theory of diathesis of cholesterol to form stones and the older ideas that the cholesterol of stones is derived from the mucosa of the gallbladder. Finally, the age-old question as to which came first, the infection or the stone, has always been answered directly one way or the other, whereas modern research has shown the answer to be a very complicated one.

In order to lay a foundation on which to build a classification, it is necessary to review rapidly a few of the facts brought to light by recent researches. Space does not permit a full discussion of some controversial matters, but reference will be made to recent discussions of them.

1. Cholesterol stones are formed during short periods of obstruction<sup>5</sup> of the cystic duct. The solvent of cholesterol, bile salts, is then absorbed from the gallbladder, while the cholesterol remains and

crystallizes.<sup>17</sup> The cholesterol of stones is derived from the bile and not from the epithelium of the gallbladder.

2. Calcium is deposited from the mucosa of the closed gallbladder, being secreted by it.<sup>18</sup>

3. The closure of the cystic duct from any cause brings on an infection of the gallbladder which lasts for a variable length of time.<sup>11</sup> During this infective period calcium is not deposited.<sup>19</sup> As the infection subsides, the deposit of calcium commences.<sup>18d</sup>

4. Infection of the gallbladder through the bile of the liver is not likely. The liver acts as a very efficient filter, and intravenous injections of enormous amounts of bacteria are necessary to produce passage through into the bile.<sup>20</sup>

5. Deposits of pigment may at least be due to a diathesis as they occur in diseases with increased pigment in the blood (hemolytic jaundice). Cholesterol stones are not associated with hypercholesteremia.<sup>21</sup>

These points are today quite well authenticated, and, as can be seen, every feature is fairly clear except the immediate exciting cause of the first period of obstruction of the cystic duct. Later obstruction may clearly be due to stones, but what causes the first one? It cannot be a diathesis, as only pigmented stones originate thus, and most gallstones do not have a nucleus of pigment. A consideration of the normal anatomy of the cystic duct will show how slight the stimulus need be. It is small, and its wall is thick, very vascular and so deeply infiltrated

17. Andrews, E.; Schoenheimer, R., and Hrdina, L.: Etiology of Gallstones: I. Chemical Factors and the Role of the Gallbladder, *Arch. Surg.* **25**:796 (Oct.) 1932. Ravdin, I. S.; Riegel, C.; Johnston, C. G., and Morrison, P. J.: Studies in Biliary Tract Disease, *J. A. M. A.* **103**:1504 (Nov. 17) 1934.

18. (a) Wilkie, A. L.: The Bacteriology of Cholecystitis, *Brit. J. Surg.* **15**:450, 1928. (b) Phemister, D. B.; Day, L., and Hastings, A. B.: Calcium Carbonate Gallstones and Their Experimental Production, *Ann. Surg.* **96**:595, 1932. (c) Phemister, D. B.; Rewbridge, A. G., and Rudisill, H.: Calcium Carbonate Gallstones and Calcification of the Gall-Bladder Following Cystic Duct Obstruction, *ibid.* **94**:493, 1931. (d) Andrews, E.; Dostal, L. E.; Goff, M. H., and Hrdina, L.: Mechanism of Cholesterol Gall-Stone Formation, *ibid.* **96**:615, 1932.

19. Andrews, E., and Hrdina, L.: Absorption of Calcium from the Gall-Bladder, *Am. J. M. Sc.* **181**:478, 1931.

20. Graham, E. A., and Peterman, M. G.: Further Observations on the Lymphatic Origin of Cholecystitis, Choledochitis and the Associated Pancreatitis, *Arch. Surg.* **4**:23 (Jan.) 1922.

21. Fox, F. W.: The Composition of Human Bile and Its Bearing on Sterol Metabolism, *Quart. J. Med.* **21**:107, 1927. Gardner, J. A., and Gainsborough, H.: Blood Cholesterol Studies in Biliary and Hepatic Disease, *Quart. J. Med.* **23**:465, 1930.

with gland and sinuses that the slight irritation would cause the swelling necessary to close it (fig. 6). Whether it is some transient infection from the blood, lymph (Graham<sup>12</sup>), liver (Andrews<sup>11</sup>) or bowel, or whether it is a chemical irritation (Mann's cholecystitis produced by surgical solution of chlorinated soda [Dakin's solution]<sup>22</sup>), or perhaps the regurgitation of pancreatic juice (Wolfer<sup>23</sup>) cannot at present be answered. Allergic disease, as recently suggested by Alvarez<sup>24</sup> and by Deissler and Higgins,<sup>25</sup> must also be considered. The important point is that this mechanism need act but once, and each subsequent attack can be explained by the stones which result from the previous ones. This is quite consonant with the fact that in our series stones were practically always present. The rare cases in which they are not found are easily explained on the basis that they have been passed or, as has already been suggested, on the basis of faulty diag-

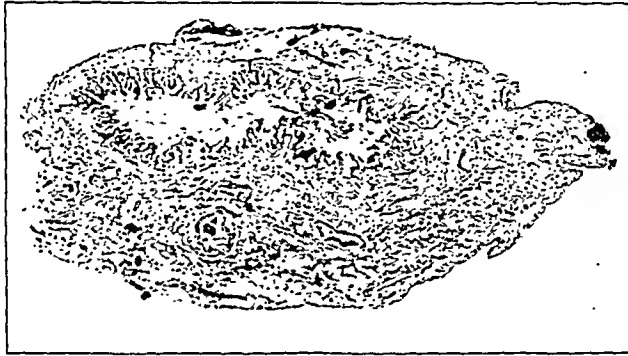


Fig. 6.—Photomicrograph showing the region of the duct of a normal gallbladder. Note the complexity of the papillae and the mucosal valves. The main artery is in close contact with the duct. Many large arterioles lie actually in and in contact with the muscular wall. It is obvious that a slight inflammatory edema or impacted stones not only would close the lumen but would compress the vessels.

nosis. While a gallbladder containing stones may show signs of severe inflammation, it is also only too true that many cases of so-called cholecystitis without stones have failed to stand the acid test of the follow-up clinic, which is the only way of ascertaining that the gall-

22. Mann, F. C.: Production by Chemical Means of a Specific Cholecystitis, *Ann. Surg.* **73**:54, 1921.

23. Wolfer, J. A.: The Role of Pancreatic Juice in the Production of Gall-Bladder Disease, *Surg., Gynec. & Obst.* **53**:433, 1931.

24. Alvarez, W. C.: Pseudocholecystitis Apparently Caused by Food-Sensitiveness, *Proc. Staff Meet., Mayo Clin.* **9**:680, 1934.

25. Deissler, K., and Higgins, G. M.: *Proc. Staff Meet., Mayo Clin.* **9**:678, 1934.

bladder was really the cause of the symptoms, which are often blamed on microscopic changes which are rather slight. Denton<sup>10</sup> found that of two hundred and fifteen gallbladders without stones, only nineteen showed definite pathologic changes.

#### AUTHOR'S CLASSIFICATION OF DISEASE OF THE GALLBLADDER

With the foregoing points in view the following classification of disease of the gallbladder is constructed. Into it may be fitted all cases without discordance in the pathologic picture and the clinical findings. Most of the older classifications have been based on the presence or absence of stones, together with the presence or absence of signs of infection, and all the other important criteria, clinical, chemical and bacteriologic, have been ignored. Recent work seems to indicate that infection is not a prominent feature. Cultures in most cases of acute and chronic cases of disease of the gallbladder yield surprisingly similar results. The finding of a normal gallbladder containing stones is commonplace. The important feature, the real factor which influences the development of the pathologic picture as well as the course of the disease clinically, is the question of the patency of the cystic duct. The following classification uses this as a basis.

##### A. Normal state of the gallbladder

Slight infiltration often seen; cholesterosis: presence or absence of stones.  
(The presence of these signs formerly often led to a diagnosis of chronic cholecystitis.)

##### B. Reaction to acute obstruction of the cystic duct

Uncomplicated type (formerly called chronic cholecystitis)

Infective type (formerly called acute cholecystitis)

Empyema (?)

Type with vascular damage (formerly acute cholecystitis)

Mild cholecystitis

Ulcerative cholecystitis

Gangrenous cholecystitis

##### C. Reaction to intermittent obstruction of the cystic duct

Normal condition between attacks

Persistent irritation (usually mild)

##### D. Reaction to chronic obstruction of the cystic duct

Uncomplicated type (formerly called chronic cholecystitis)

Acute reinfection

Mild

Empyema (?)

Hydrops

##### E. Reaction to obstruction of the common duct

Acute or recent type (dilated and thin-walled gallbladder)

Chronic type (shrunken and fibrosed gallbladder)

##### F. Neoplasms

Our own observations are in accord with those of Denton and of Feinblatt,<sup>9</sup> i. e., that the underlying lesion is in most cases vascular. Denton quite aptly likened acute cholecystitis to a hemorrhagic infarct. The predominating factors in the picture are edema, hemorrhage and infiltration, with large and small mononuclear cells. Thromboses are not common, but the veins especially are dilated. Most students recognize that the tortuous venous plexus (anatomic studies by Karlmark<sup>26</sup>) about the cystic duct is the vulnerable point and that the arteries run somewhat farther off and are not so liable to injury. Whether the process is initiated by an impacted calculus or by edema from some other source, the results are the same and the clinical syndrome produced is the same.

*A. Normal State of the Gallbladder.*—Infiltration of the gallbladder with lymphocytes is normal. Control specimens both from animals and human beings show that a few patches may occur. Lymphoid follicles in the submucosa may be numerous (fig. 4). It is a question if the few cases with extensive pure lymphoid infiltration may not be included in this group. Cholesterosis is common.

The bile is acid. Its  $p_H$  lies between 6.8 and 7 in the ordinary case in which the patient has been starved for from twelve to fifteen hours before operation. Drury, McMasters and Rous<sup>27</sup> have shown that the gallbladder progressively acidifies bile that lies in it. Their figures for the bile from dogs as well as those for many of our own cases lie considerably more on the acid side. While gallbladders with patent ducts, irrespective of their condition, have contained bile in this  $p_H$  range, that of the bile from diseased gallbladders has varied widely. The bile from three cases of diseases of the gallbladder in human beings with a high calcium content typical of an obstructed gallbladder has shown a  $p_H$  considerably more alkaline, while in other cases, especially in the active stage, the figures have been lower. Sufficient material is not at hand to make it possible to draw definite conclusions, but one is tempted to assume that the acutely (recently) obstructed gallbladder acidifies the bile rapidly and that after prolonged obstruction, when the reaction has subsided, alkalization takes place. This, of course, fits in with the deposit of calcium in such cases,<sup>18b</sup> as calcium is less soluble in alkaline solutions. It contains no cholesterol crystals or undissolved amorphous cholesterol. It contains from 20 to 50 mg. per hundred cubic centimeters of calcium. The white cell count of the bile ranges from 2,000 to 5,000 per cubic centimeter. The cholesterol content of the bile

26. Karlmark, E.: Die Lokalisationstendenz bei Metastasierung durch die Venen in die Leber, *Acta path. et microbiol. Scandinav.*, supp. 13, 1932, p. 1.

27. Drury, D. R.; Rous, P., and McMaster, P. D.: Some Causes of Gallstone Formation: III. Relation of Reaction of Bile Experimental Cholelithiasis, *J. Exper. Med.* **39**:403, 1924.



is less than one-thirteenth the bile salt content. The cystic duct is patent. (We have never observed cholesterol crystals in true liver bile.) Streptococci, staphylococci, *Bacillus Welchii*, *Bacillus coli*, *Bacillus typhosus* and other kinds of bacteria are frequently present, but in small numbers (under 200 per cubic centimeter). The wall may or may not contain the same flora.

*B. Reaction to Acute Obstruction of the Cystic Duct*—Uncomplicated Type: The characteristic feature in the gallbladder in which the disease arises from acute obstruction of the cystic duct is edema, which is most marked in the outer coats. There is an invasion, most marked in the outer coats of many round cells, and a relatively small number of polymorphonuclears. Eosinophils appear in large numbers as the process subsides. The cystic duct is closed. The fluid often contains cholesterol in crystals or in amorphous form. The calcium content is lowered. The bacterial count falls within the normal range, and culture of both bile and the wall may be sterile. The bile salt content is markedly lowered.

*Infective Type*: In this type there is a dense infiltration of all the layers of the gallbladder with polymorphonuclear leukocytes. Edema and thickening of the wall are more pronounced, especially in the subserous layers. The bacterial count will be enormously raised, especially in the stagnant bile. There is little or no increase in the cells in the bile. *B. coli* is a common finding in such cases.

*Type With Vascular Damage*: There are marked edema and thickening of the walls of the gallbladder, which are indistinguishable from these changes in the infective type. The infiltration, however, has far fewer polymorphonuclears except in the subsiding stages, when eosinophils are numerous. In addition, there are marked venous hyperemia and marked dilatation of the numerous lymphatic channels, especially in the subserous layers. The bacteriologic picture is normal, and sterile cultures are not uncommon. The mucosa is intact. Cholesterol crystals are common, and the calcium content is low. The bile salt content is also lowered markedly. Stones may or may not be present.

It is quite clear not only from our own findings but also from the recent literature indicating that cholecystectomy in the acute stage of disease of the gallbladder is usually safe that this type and not the infective type is the usual one in cases of so-called "acute cholecystitis." While I know of no means of differentiating these two groups preoperatively, it is interesting to note that Feinblatt's<sup>9</sup> studies of the cause of death following cholecystectomy showed that of twenty-three deaths none were due to acute peritonitis.

*Ulcerative Cholecystitis*: This condition is a complication of the type of disease of the gallbladder in which there is vascular damage.

Typical ulcers are rare. Most ulcers are really artefacts. Before making the diagnosis one should assure oneself that the gap in the mucosa is in reality lined with a pyogenic membrane. In view of the fact that ulcers have not been found except in the acute types of cases, we are justified in concluding that unless rupture takes place they heal rapidly with minimal scar formation, as even the scar of an ulcer has not yet been found in a quiescent case in our serial sections.

**Gangrenous Cholecystitis:** This type consists of a more extensive lesion of the vascular supply than that found in the ulcerative type. Thromboses in the vessels follow stasis, and necrosis, either total or partial, of the walls permits rupture. This being a complication which occurs only after acute obstruction of the cystic duct, in most cases much of the toxic bile salt content<sup>28</sup> has been absorbed and biliary peritonitis does not occur, but instead a walled-off abscess, usually containing necrotic material but no true pus.

**C. Reaction to Intermittent Obstruction of the Cystic Duct.**—The ability of the gallbladder to return to a normal state after the reactions of acute obstruction is interesting. Many cases have come to our observation in which severe repeated attacks of colic have left little doubt as to the diagnosis but in which an operation performed between attacks has disclosed a gallbladder with stones which was normal in every other way. Although in our microscopic studies we constantly searched for it, we could find no correlation between muscular hypertrophy and this factor. One fact, however, is striking. If the tables are examined it can be seen that there is a definite relationship between the patency of the duct and the extent of the pathologic process. The degree of infiltration is arbitrarily graded as 1, 2, 3 or 4 plus. If the average for the active and quiescent cases of disease of the gallbladder is found, one sees that the active cases average about the same as the quiescent cases (about 1.8 plus). However, if the cases in both groups are studied in relation to obstruction of the cystic duct, the surprising fact emerges that those with closed ducts (thirty-six) average 3 plus infiltration and those with patent ducts (twenty-two) average 0.5 plus.

These findings indicate clearly that the tendency of the gallbladder is to return to normal soon after an attack, providing that the duct reopens and that findings of residual infection indicate that the reestablishment of the flow of bile is faulty. This is probably the condition in the "grumbling gallbladder."

**D. Reaction to Chronic Obstruction of the Cystic Duct.**—In this type fibrosis of the wall of the gallbladder is marked. The mucosa is

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28. Horrall, O. H., and Carlson, A. J.: The Toxicity of Bile, *Am. J. Physiol.* **85**:591, 1928. Rewbridge, A. G., and Hrdina, L.: Etiological Rôle of Bacteria in Bile Peritonitis, *J. Exper. Biol. & Med.* **27**:528, 1930.

intact but often atrophied, with small sessile villi. There may or may not be marked thickening, but if there is, it is chiefly in the subserosa. The infiltration is mostly of mononuclear types, and fibroblasts are common. The contents are often sterile, and the bacterial count is low, comparable to the normal value. The bile salts and pigment are absorbed from the bile, the former rapidly, in from two to four weeks, and the latter in from three to six months. The contents are thick. Cholesterol if still present is not in solution. The calcium content is very high, and often much amorphous calcium carbonate is precipitated. The reaction is alkaline. Stones may or may not be present.

**Acute Reinfection:** That this complication takes place is shown by cases with "white bile" and signs of acute or subacute infection. There is an increase in the amount of infiltration, which is composed of polymorphonuclear cells and a lowering of the  $p_H$  of the fluid content.

**Hydrops:** Obviously this is a complication of chronic obstruction of the cystic duct, but just why the secretion of the mucosa of the gallbladder should be different in these cases is unknown. Clearly atrophy of the mucosa is the important element, but we are unable to state what the cause of the atrophy is.

**Empyema:** This might, of course, occur as a complication of either acute or chronic obstruction of the duct. The lack of such a case in our series and the proof that many apparent empyemas<sup>29</sup> are simple accumulations of cholesterol or calcium is not proof that it never occurs.

#### SUMMARY

A study is reported of one hundred and sixteen surgically excised gallbladders, fifty-five of which were sectioned serially at intervals of 2 cm.

There was a total lack of the proper correlation between the pathologic classification of these cases and the clinical and bacteriologic findings.

The severely inflamed gallbladder contains about the same flora as the normal or quiescent one. It is very often sterile.

The degree of inflammation of the gallbladder is always greatest in the outer layers.

Edema plays the most prominent part.

The degree of inflammation is not dependent on the number of bacteria in the wall or in the bile. It is dependent on the patency of the cystic duct.

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29. Feinblatt.<sup>9</sup> Denton.<sup>10</sup>

Fever probably originates from partial obstruction of the common duct, not in most cases from absorption of toxins or bacteria from the gallbladder itself.

In most so-called empyemas of the gallbladder the "pus" is really precipitated calcium or cholesterol.

A new system of classification is proposed based on physiologic features in which the pathologic feature fits harmoniously into the bacteriologic, chemical and clinical picture.

# ESSENTIAL HYPERHIDROSIS CURED BY SYMPATHETIC GANGLIONECTOMY AND TRUNK RESECTION

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Essential hyperhidrosis is excessive sweating which is limited to circumscribed bilaterally symmetrical areas and to extremities. Excessive sweating of the hands and feet frequently accompanies vasospastic conditions, such as are seen in Raynaud's disease and peripheral atrophic arthritis, but in true essential hyperhidrosis the patient complains chiefly of excessive perspiration that is aggravated by exposure to warm temperatures, by nervous excitement and by emotional strain. This symptom becomes so annoying as to interfere with business and social activities. When the hands are involved, the patients find it impossible to work as bookkeepers or accountants or to work with delicate fabrics that require dry finger-tips. The skin over the finger-tips often becomes macerated and tender. The patients are likewise constantly embarrassed in meeting strangers, since their hands are always dripping wet and they feel compelled to apologize in offering them in the customary salutation. They frequently shun the opposite sex to avoid embarrassing situations. The constantly wet hands soil gloves and ruin fine dress fabrics.

## ANATOMY

The secretory nerve fibers to the sweat glands originate in the thoracolumbar portion of the sympathetic system. The terminal neuron to a sweat gland is a postganglionic gray ramus that leaves one of the ganglions in the thoracolumbar chain to reenter the spinal nerve, there to be distributed to the corresponding dermatome of the musculocutaneous segment. This fiber is so intimately entwined with the corresponding sympathetic fibers to the sebaceous glands, pilomotor muscles, arterioles and capillary system of the same segment that it is impossible to separate it from these accompanying fibers. Therefore, any interruption of sympathetic trunks or rami that will produce a vasodilatation of arterioles and capillaries will produce loss of sweating, reduction in sebaceous secretion and paralysis of pilomotor muscles.

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From the Section on Neurologic Surgery and the Division of Medicine, the Mayo Clinic.

Read at the meeting of the Western Surgical Association, St. Louis, Dec. 7 and 8, 1934.

## PHYSIOLOGY

Sweating and vasodilatation are physiologic responses to the central heat-regulating mechanism. Excessive bodily heat can be reduced by vasodilatation of the arteries and capillaries of the skin and by sweating, as vasodilatation allows more blood to flow to the surface of the body and the evaporation of sweat cools the surface of the skin, both of which lower the temperature of the blood before it completes its arterial circuit.

Because the sympathetic fibers to the peripheral arterial system and those to the sweat glands are so intimately associated and because the two structures appear to have one primary function of regulating bodily temperature, it is only natural that dysfunction of one would bring about an accompanying dysfunction of the other. Therefore, one is not surprised to find the skin of the hands and feet soaked with sweat in cases in which patients suffer from Raynaud's disease. Excessive perspiration does not accompany the stage of blanching but accompanies the partial compensatory phase following asphyxia.

Sweating, though a normal physiologic response, varies with each person. It is normally more excessive among obese persons and those who are excessive eaters, since more heat is generated by the increased metabolism. The excessive sweating of patients with hyperthyroidism is explained on a similar basis. The activity of the sweat glands varies also in the individual case, since some persons perspire more profusely on the face than on the body or feet.

## PATHOLOGY

Excessive sweating is not considered a pathologic symptom unless it interferes with business and social activities. When it accompanies vasomotor disturbances, such as Raynaud's disease, it is promptly relieved when successful sympathetic ganglionectomy and trunk resection are performed to relieve the vasomotor spasm, and it therefore needs no special consideration. Excessive perspiration of the feet is a rather common phenomenon, but rarely is it so severe as to require surgical treatment. When excessive sweating of the feet is accompanied by unpleasant odors (bromidrosis), patients frequently seek relief, and Waring<sup>1</sup> has found the following preparation a useful dusting powder:

Pulvis acidi salicylici	
Pulvis zinci carbonatis praecepitati	
Pulvis magnesi ustae aa	4 drachms (7.09 Gm.)
Pulvis amyli	15 drachms (26.6 Gm.)
Pulvis talcis	20 drachms (35.4 Gm.)

1. Waring, J. B. H.: Hyperhidrosis, *Virginia M. Monthly* 58:250 (July) 1931.

He suggested that this be used following frequent changes of the hose and after washing the feet. When this fails to produce the desired results, operation on the sympathetic nervous system is indicated (fig. 1).

As has been stated, essential hyperhidrosis is a syndrome characterized by excessive sweating in circumscribed bilateral areas and in the extremities of persons who do not complain of peripheral vascular disease.

#### ETIOLOGY

It is rather difficult to offer an adequate explanation for the appearance of essential hyperhidrosis. Pieri<sup>2</sup> classified hyperhidrosis, in the

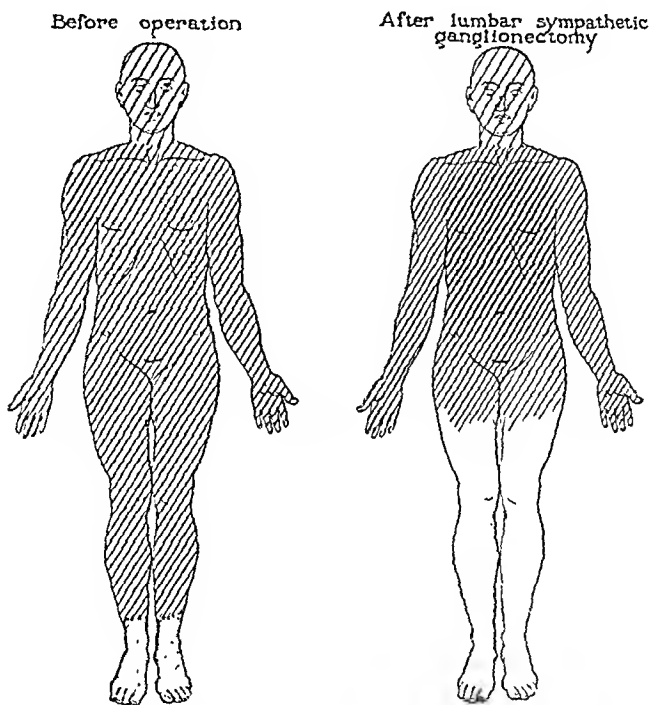


Fig. 1.—Diagram showing the therapeutic effect of bilateral lumbar sympathectomy and trunk resection, including the second, third and fourth lumbar ganglions. The intensity of shading indicates the degree of perspiration that occurred.

report of his five cases, into three types. The first type he referred to as sympathetic hyperhidrosis, occurring secondary to involvement of other organs and resulting from dysfunction of the nervous system. The second type he referred to as functional hyperhidrosis, which is an exaggeration of the normal sweating function. The third type he called idiopathic hyperhidrosis and included cases in which he has been unable to establish the origin of the hyperhidrosis.

2. Pieri, Gino: Contributi alla chirurgia del sistema nervoso vegetativo; la cura della iperidrosi, Arch. ital. di chir. 31:117 (Feb.) 1932.

Roberts,<sup>3</sup> in an ably presented review of a case of hyperhidrosis and cyanosis which was relieved by sympathectomy, stated that the responsibility for the morbid condition lay not in the central nervous system but in the mesenchymal cells that surround the capillaries of the derma. Roberts further expressed the belief that these pericapillary zones are physiologically distinct from the differentiated parts of the derma, and he agreed with authorities who ascribed to the undifferentiated cells of these zones peculiar properties; not only are they the mother cells, out of which are derived the endothelial cells, but they control the behavior of the capillaries, causing their expansion or contraction and maintaining the general tone of the capillary bed. He expressed the opinion that this control is chemical or physicochemical rather than nervous and that the nerve impulse is merely the trigger that starts the dermal reactions.

Functional hyperhidrosis of Pieri consists of excessive normal sweat responses. We suspect that Pieri included in this group of patients with sympathetic hyperhidrosis those who had excessive sweating accompanying vasomotor diseases such as Raynaud's disease. Judging from Roberts' review, it appears that his case would fall in the same group as does the case reported by Leriche and others<sup>4</sup> and cases of ours in which patients sought relief primarily for the symptoms of Raynaud's disease or the pains of atrophic polyarthrititis of the hands and feet. Roberts' explanation of the phenomenon of excessive hyperhidrosis in these cases of sympathetic hyperhidrosis corresponds in a general way with the explanation offered by those who believe that Raynaud's disease is the result of a peculiar property inherent in the mesenchymal cells or the dermal arteries. However, the other school of thought still holds that the nervous control plays a more important part than mere trigger function, since interruption of this nervous control by sympathetic ganglionectomy and trunk resection completely abolishes the function of sweating in the somatic segment thus innervated. Increased temperature, nervous excitement and emotional strain no longer are capable of producing sweating in the denervated somatic segment. If sweating and vasomotor control were governed by the peculiar properties of these mesenchymal cells, one would expect a certain degree of sweating to continue when the patient encountered stimuli that produced sweating before operation.

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3. Roberts, H. L.: The Removal of the Inferior Cervical Ganglia and Its Effect on Hyperhidrosis and Cyanosis of the Hands and Feet, *Brit. J. Dermat.* **46**:126 (March) 1934.

4. (a) Leriche, R., and Arnulf, G.: Effets de diverses sympathectomies sur la sudation, *Bull. et mém. Soc. nat. de chir.* **60**:354 (March 3) 1934. (b) Leriche, R., and Frieh, P.: Hyperhydrose extrêmement prononcée des mains et des pieds: Essai de traitement par des opérations sympathiques, *Lyon chir.* **31**:86 (Jan.-Feb.) 1934.



To substantiate further the proof that sweating is a response to the central heat-regulating mechanism and is controlled by central influence, we refer to cases in which patients underwent sympathectomy and in which it was observed that the amount of sweat secreted was greatly increased in areas of skin not affected by the operation. This excessive secretion of sweat between the areas deprived of sympathetic innervation, we believe, represents an increased response to the normally innervated area from the heat-regulating center, in order to maintain

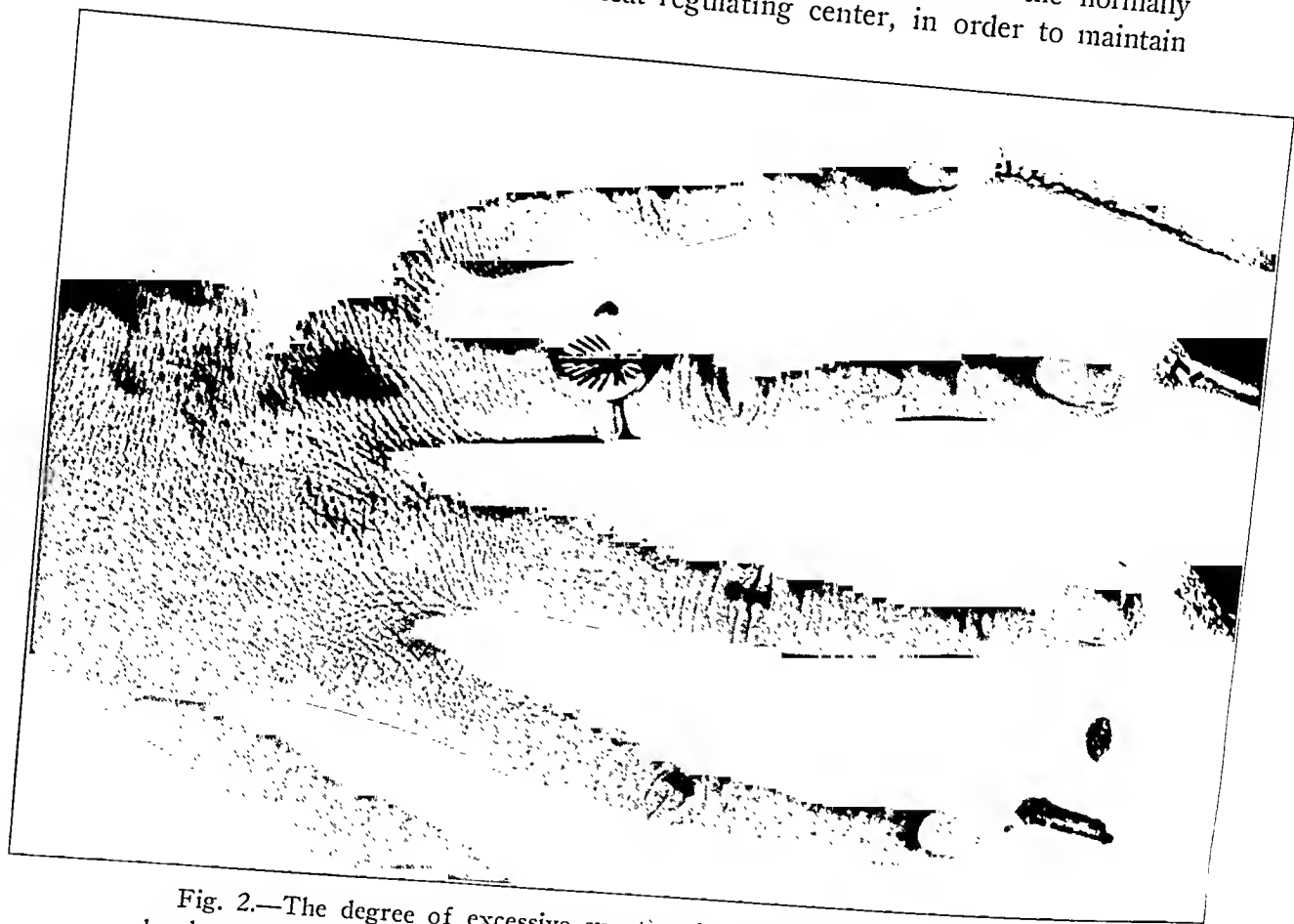


Fig. 2.—The degree of excessive sweating is illustrated by the appearance of droplets on the fingers and streams of perspiration running from the finger-tips during the interval while the photograph was taken.

normal bodily temperature. Though the sweat contains waste products, it does not mean that the body is dependent on this secretion for elimination when the kidneys still function normally.

For the idiopathic type we suggest the name "essential hyperhidrosis," and we include in this type the condition presented by patients who complain chiefly of excessive sweating that interferes with their work and social activities (figs. 2 and 3). We further believe that this type of hyperhidrosis results from dysfunction of the sympathetic nervous system, a dysfunction not unlike that of Raynaud's disease.

which originates in the higher cerebral centers, and that the act of sweating is only a response to a central stimulus.

#### TESTS FOR SWEATING

The routine procedure consists of placing the patient in a warming chamber and exposing the entire nude body to an environmental temperature of approximately 120 F. The intensity and distribution of the sweating are noted and quantitated. After operation similar studies are carried out, using test papers of cobalt blue. These are placed on the skin of the face, neck, thorax, arms and fingers following cervicothoracic operation. To test the completeness of lumbar ganglionectomy, test papers are placed on the skin of the lower part of the abdomen and on the legs and toes. The blue color of the testing paper changes to pink

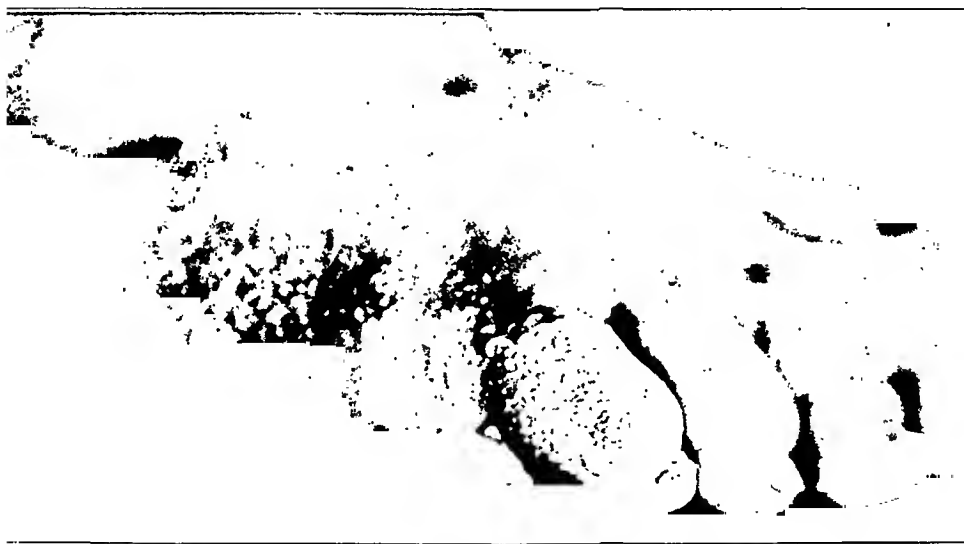


Fig. 3.—Hyperhidrosis of the toes and foot.

in the presence of slight degrees of sweating. This outlines the thoroughness and the extent of the sympathectomy.

Another method of testing is accomplished by the administration of pilocarpine in doses of  $\frac{1}{40}$  grain (0.006 Gm.) and indicates the functional activity of the sweat glands. This drug acts directly on the sweat glands. Tests carried out within one month after operation usually show that sweating can be induced by this drug. Months after the operation, the peripheral effects of pilocarpine gradually diminish and sweating is entirely absent.

#### REPORT OF CASES

CASE 1.—A man,<sup>5</sup> aged 27 years, a clerk for an oil company, complained of excessive sweating of the palmar surfaces of both hands and the solar surfaces of

5. Adson, A. W., and Brown, G. E.: Extreme Hyperhidrosis of the Hands and Feet Treated by Sympathetic Ganglionectomy, *Proc. Staff Meet., Mayo Clin.* 7:394 (July 6) 1932.

the feet of seven years' duration. Sweating was more marked in the summer and in heated rooms during the winter. During the summer the hands became excessively wet, and the constant sponging necessary caused desquamation of the outer layers of the skin. Fissures developed between the finger folds, and it was practically impossible to use the fingers because of the burning and distress of the desquamated skin. Each year the condition had become worse, and this made the patient exceedingly nervous and irritable.

The patient was examined on a moderately warm day, at which time the hands were wet to a rather abrupt line at the wrist and the feet to the level of the malleoli. The hands and feet were slightly puffed, and the skin on the palms was slightly denuded. Sweating of the feet had not started until sweating of the hands became marked. Various known medical measures had been tried for five years

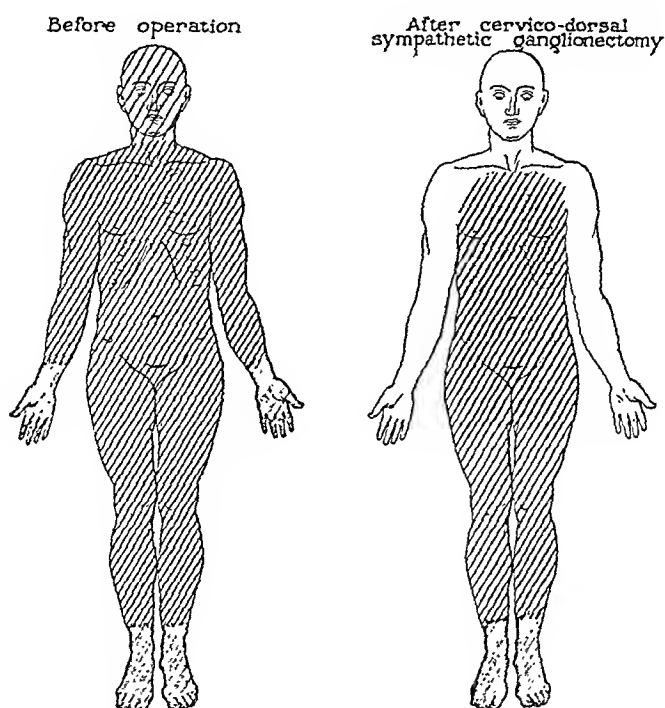


Fig. 4.—The intensity of shading illustrates the degree of perspiration that occurred before the operation, and the absence of shading over the face, neck, arms and hands illustrates the therapeutic effects of sympathectomy.

previously but without avail. The patient was greatly depressed mentally during the summer months, and he faced the hot weather with dread. The condition constituted a true disability, and the patient insisted that measures be taken to control it as it was seriously interfering with his livelihood.

General examination gave normal results. The diagnosis in this case was hyperhidrosis of the hands and feet. The condition was bilateral and symmetrical on the four extremities. The distribution and mode of onset strongly suggested a primary disturbance of the cerebral sympathetic center, since such limited areas were involved.

Bilateral cervicothoracic ganglionectomy and trunk resection by the posterior approach was performed on June 17, 1932. All communicating rami, with the brachial nerves, were interrupted in addition to resection of the trunk and ganglions. The patient's recovery was uneventful. The hands were perfectly dry following operation (fig. 4).

Sweating tests were carried out fourteen days after operation in a heat chamber (120 F.), strips of cobalt blue paper being used as indicators for minimal degrees of sweating. There was complete absence of sweat on the upper part of the thorax, head, arms and hands. Sweating of the dorsal surfaces of the feet was profuse; of the plantar surfaces, mild. There was sweating in all areas following administration of  $\frac{1}{40}$  grain (0.006 Gm.) of pilocarpine. The average surface temperatures of the fingers increased 1 C., and Horner's syndrome was complete and equal on the two sides. The patient's general condition was excellent, and improvement in his mental condition was striking. The surgical result has continued to remain successful.

CASE 2.—A girl, aged 18, for the past thirteen years had suffered from excessive sweating of the hands and, to a lesser degree, of the feet. This had begun



Fig. 5.—Maceration of skin on the palmar surface of fingers and palm from excessive sweating, as well as the degree of hyperhidrosis indicated by streams of sweat leaving the fingers during the interval of time required to make the photograph, may be noted.

following mastoidectomy on the right side. The feet and hands were objectively cold most of the time, and at times the hands revealed small red papules; in winter they cracked and became painful. She had suffered from headaches for the past three or four years, and these had occurred almost daily; they were relieved by acetylsalicylic acid. Her hands perspired practically all the time; they were especially affected when she was nervous about meeting people. In hot weather spontaneous attacks had occurred.

The patient's blood pressure in millimeters of mercury was 114 systolic and 76 diastolic. General examination otherwise gave normal results. A diagnosis of

essential hyperhidrosis was made, and operation was carried out on Nov. 14, 1933, at which time bilateral cervicothoracic sympathetic ganglionectomy was performed. The wound healed by primary intention. Convalescence was uneventful except for the complaint of pains in the arms and shoulders. The patient's hands were warm and dry at the time of her dismissal. In a letter written in June 1934 she stated that she was completely relieved of hyperhidrosis and was enjoying life as never before (figs. 5 and 6).

CASE 3.—A man, aged 35 years, complained of excessive sweating of the hands, which he had noted since childhood. This condition was noticeably worse when he became excited. He had also noticed cracking and burning of the hands. His feet were cold but did not perspire excessively. He was a very ambitious, energetic type of man and had entered an engineering school; however, because

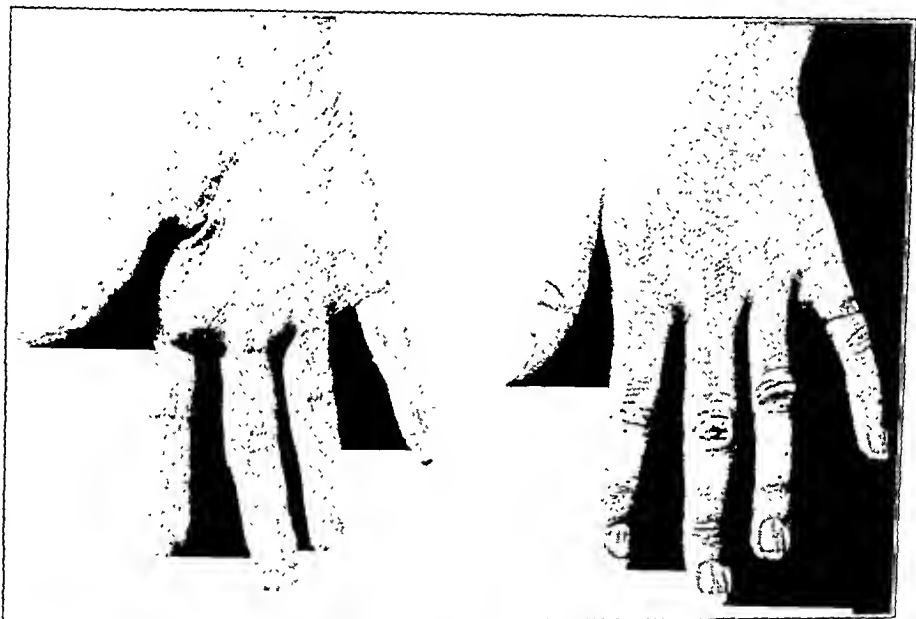


Fig. 6.—The effect of cervicothoracic sympathetic ganglionectomy and trunk resection in preventing excessive perspiration and in restoring the condition of the skin of the patient's hands illustrated in figure 5.

of the excessive sweating of his hands, he was unable to finish his course in draftsmanship, and consequently he was forced to leave school. He became an automobile salesman but found it exceedingly difficult to write letters or to sign checks on account of this excessive perspiration.

General examination gave normal results except for mild hypertension, the blood pressure in millimeters of mercury being 140 systolic and 90 diastolic. A diagnosis of excessive hyperhidrosis of both hands was made, and on Nov. 3, 1933, bilateral cervicothoracic sympathetic ganglionectomy was performed. Following operation, the wound healed by primary intention, convalescence was uneventful, and there was complete cessation of sweating of the hands. The patient returned home completely relieved. Ten months after taking a 3,000 mile automobile trip, he stated that his hands were completely free from excessive perspiration and that his general condition was excellent. He is one of the most grateful patients we have ever had.

CASE 4.—A man, aged 25 years, registered at the clinic on Feb. 28, 1934, complaining of excessive sweating of the feet and hands. When he was about 8 or 9 years of age he had noticed that after a few minutes' exposure of his face to cold his cheeks would turn red, purple and white and would begin to swell. When he returned to a warm room this condition would be entirely relieved. At about the age of 12 years he began to notice excessive sweating of the hands and feet. At the age of 18 he began to have sick headaches on one or the other side of his head. They were worse in hot weather and could be brought on by a jar. He had scotoma and nausea but no vomiting. Gradually developing throughout this course he had had increasing nervousness and fatigue.

General and neurologic examinations revealed no organic lesions except for a blood pressure in millimeters of mercury of 140 systolic and 85 diastolic. Dr. E. V. Allen, consulting internist, made the following note summarizing the report of the examination: "The syndrome is 'sympatheticotonia' expressed by nervousness, hyperhidrosis, a tendency to hypertension, palpitation and vascular instability. The patient has migraine, exhaustion, cold wet hands and feet, vasomotor changes in the hands, pallor and swelling on exposure of the face to cold and vasomotor rhinitis and duodenitis."

Bilateral cervicothoracic sympathetic ganglionectomy was done on March 8, 1934. The patient's postoperative course was uneventful, and the wound healed by primary intention. Immediately following the operation the hands were warm and dry.

In a letter written on Nov. 20, 1934, the patient stated that he had been free from sweating of the hands, arms and head but had had more than usual on his back. Headache and migraine had disappeared, except for a slight ache back of his eyes which lasted only thirty minutes and occurred only at night. He still complained of nervousness, fatigue, redness of the eyes on waking and rhinitis.

CASE 5.—A South American man, aged 22, complained of excessive sweating of the hands and of burning gastric pains. General examination revealed no evidence of organic gastric disease. Hyperhidrosis of the hands had been gradually progressive for a number of years. The condition was much worse in hot weather and was aggravated by nervousness. In view of the fact that he was an engineering student, excessive perspiration of the hands interfered to a great extent with his work on books and paper. The skin on the palmar surfaces was wet, soft, mushy and red. Beads of sweat stood out in droplets on this palmar surface. The patient's feet were slightly affected, but not nearly so severely as his hands.

Bilateral cervicothoracic sympathetic ganglionectomy was performed on August 30, 1934. During his convalescence the patient complained of Horner's syndrome and of pain in the ulnar aspect of each arm. The wound healed by primary union. The aching pains in the arms disappeared in three weeks, although Horner's syndrome will continue permanently. He became accustomed to it and did not complain further when he learned that his vision was not impaired. His hands promptly became dry following the operation, which he stated more than compensated for the pain he suffered.

The review of these five cases reveals that the chief symptom was that of hyperhidrosis which affected the hands and fingers. Four men and one woman had this symptom; all of them were of the asthenic type, and none of them complained of cyanosis of the fingers. All of them, however, had vasomotor instability in that their hands were either hotter or colder than the examiner's hand. In most instances the skin

on the palmar surface was bright pink or almost red. Patients with this condition, as is also the case with patients who have Raynaud's disease, frequently exhibit other disturbances of the autonomic nervous system. Functional disorders of the gastro-intestinal tract, fatigued states, vasomotor rhinitis and vasomotor instability with poor adaptation to environment are common expressions of sympathetic imbalance. The primary abnormality suggests an origin in the central nervous system. This conception is strengthened by observations recently made in two cases. In one case<sup>6</sup> a boy for ten years during his waking hours exhibited a rhythmic fall in bodily temperature to levels as low as 91 F. This



Fig. 7.—Appearance of skin, hair follicle and sebaceous and sweat glands taken from the forearm of a patient who had undergone cervicothoracic sympathetic ganglionectomy for Raynaud's disease fifteen months prior to the biopsy ( $\times 75$ ).

periodic hypothermia was associated with profuse generalized hyperhidrosis. The probable etiologic factor in this case was encephalitis, which had affected both the temperature and the sweating centers. Control of sweating did not modify the hypothermia, but when amytal was given, or when the patient was asleep, the central irritability was controlled, with return of temperature to normal levels and disappearance of hyperhidrosis. A second patient, a boy with anhidrosis, presented features of erythromelalgia. The extremities were hot and painful

6. Hines, E. A., Jr., and Bannick, E. G.: Intermittent Hypothermia with Disabling Hyperhidrosis: Report of a Case with Successful Treatment, *Proc. Staff Meet., Mayo Clin.* 9:705 (Nov. 21) 1934.



Fig. 8.—Higher magnification of figure 7, illustrating slight increase in fibrous tissue with no other change ( $\times 175$ ).

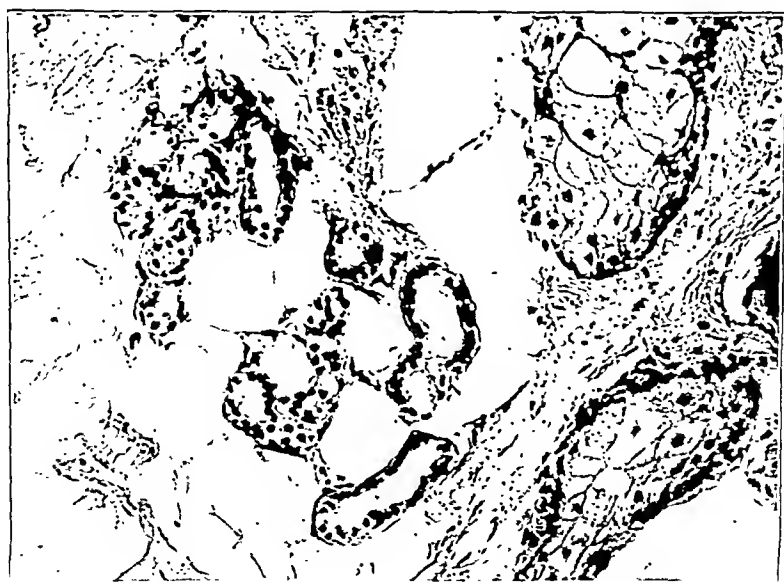


Fig. 9.—Higher magnification of sebaceous and sweat glands in figure 7, revealing no atrophy or change from the normal although a successful interruption of postganglionic rami has been effected by cervicothoracic sympathetic ganglionectomy.



when exposed to room temperatures. The absence of heat radiation from the lack of sweating created local areas of hyperthermia, with distressing, disabling symptoms. The etiology of this disease was not clear, but there was a suspicion that a cerebral disease had affected the sweating centers (hypothetic); at least, there was no evidence that any peripheral dysfunction was the primary disorder.

The cures effected by removal of the sympathetic control in cases of Raynaud's disease and of localized forms of hyperhidrosis furnish strong evidence of an abnormality referable to the central nervous system in these disorders (figs. 7, 8, 9 and table).

*Hyperhidrosis: Surface Temperatures (Degrees, C.) \**

Case	Operation	Digits						Comment
		R <sub>1</sub>	R <sub>3</sub>	R <sub>5</sub>	L <sub>1</sub>	L <sub>3</sub>	L <sub>5</sub>	
1	Before	28.4	28.5	28.7	29.0	29.2	28.7	Complete operation
	After	35.7	35.8	35.7	35.8	36.0	35.7	
2	Before†	....	....	....	....	....	....	Complete operation
	After	33.3	34.1	34.5	35.3	35.4	35.7	
3	Before†	....	....	....	....	....	....	Complete operation
	After	33.4	34.6	34.5	34.3	34.7	34.6	

\* Readings of surface temperatures were taken with an electrothermocouple from the skin over the first, third and fifth fingers of each hand, before and after the completion of cervicothoracic sympathetic ganglionectomy and trunk resection. R indicates right; L, left.

† No readings obtained before operation.

#### SUMMARY

Essential hyperhidrosis affecting the hands and feet is frequently a most disabling disease and seriously interferes with the patient's ability to earn a livelihood. Observations indicate that the severity of the condition and the areas involved by the excessive sweating are controlled by a cerebral influence. Complete cure is effected by sympathetic ganglionectomy.

# OSGOOD-SCHLATTER'S DISEASE

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AND

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In the diagnosis of Osgood-Schlatter's disease both clinical and roentgenographic features must be evaluated. The information revealed by roentgenograms is often clearcut and convincing. However, it seems that anatomic variations in the tibial tubercle are too often regarded as pathologic.<sup>1</sup> On reviewing the roentgenograms of several hundred knee joints of children, adolescents and young adults who had no clinical complaints referable to this region, we observed variations in the size, shape and manner of growth of the tubercle. Furthermore, it is important to remember that no unusual thickening of the attachment of the patellar ligament into the tibial tubercle is observed roentgenographically (fig. 1*A* and *B*). With these safeguards in mind, we attempted to establish the criteria by which roentgenographic diagnosis of Osgood-Schlatter's disease can unequivocally be made, so that anatomic variations will not be misinterpreted.

We found on examining the roentgenograms made in 106 cases<sup>2</sup> of Osgood-Schlatter's disease that thickening of the patellar ligament at

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1. Palugyay, J.: *Fortschr. a. d. Geb. d. Röntgenstrahlen* **35**:595 (Jan.) 1927.

2. These 106 cases from the orthopedic services are from a group of 120 in which the diagnosis was Osgood-Schlatter's disease, 14 of which were not considered instances of this condition after restudy. In this group of 106 cases, the right knee was involved in 40, the left knee in 48 and both knees in 18. Ninety-nine of the patients were males. Ten were adults varying in age from 21 to 45 years who presented islands of bone (roentgenographic picture) in the patellar ligament, with occasional symptoms of pain and swelling about the tibial tubercle (non-healed type of Osgood-Schlatter's disease). The remaining 96 patients were divided into the following age groups:

Age	9	10	11	12	13	14	15	16	17	18 years
Male .....	2	1	10	14	30	26	4	3	..	1
Female .....	1	1	1	1	1					

In this group of 106 patients, 40 per cent cited trauma as relevant to the presenting symptoms, 25 per cent were not certain of any preexisting trauma, and 35 per cent gave no evidence of any trauma.

its insertion was a fairly constant if not an invariable sign of disease in that region (fig. 1C). In fact, such a swelling was occasionally observed roentgenographically even prior to the finding clinically of a mass of soft tissue in the region of the tubercle (fig. 2A). Next in importance is the presence of irregular calcific spicules radiating from the anterior surface of the tubercle (fig. 2B). As the lesion progresses they may extend for some distance into the patellar ligament. Furthermore, small or large fragments of bone avulsed from the anterior surface of the tubercle were also to be found in the patellar ligament (fig. 2C). Islands of bone were seen in the patellar ligament at a considerable distance above the lowest point of the tibial tubercle (fig. 3A). These may have



Fig. 1.—A, a roentgenogram of the right knee of a boy 13 years old which shows defects in the tibial tubercle. The absence of soft tissue swelling in this region precludes a diagnosis of Osgood-Schlatter's disease. Note that all the photographs of the roentgenograms are reproduced dark in order to show clearly the soft tissues. B, a roentgenogram of the right knee of a boy 13 years old which shows a separate center of ossification; no soft tissue swelling is noted. C, a roentgenogram of the left knee of the same boy (fig. 1B) reveals a separate center of ossification for the tubercle with a definite soft tissue swelling. The diagnosis was Osgood-Schlatter's disease.

formed there or may have been fragments which were avulsed from the tubercle. In most of our cases the epiphyseal plate between the tubercle and the tibial metaphysis was not unusually widened. In some the distal tip of the tubercle pointed toward the region of the knee joint.

Clinically, most of our 106 patients with Osgood-Schlatter's disease complained either of constant or of intermittent pain, or of discomfort about the knee. They frequently were aware of a mass in the region of the tibial tubercle. Clinical examination revealed soft tissue swellings in the region of the tibial tubercle in about 90 per cent of our patients. In several instances, in spite of advanced roentgenographic changes in the tibial tubercle no localized tenderness was noted. Motions of the knee were free. In many patients flexion of the knee caused tenderness over the tibial tubercle.

The review of our roentgenograms showed the pathologic changes of Osgood-Schlatter's disease to occur in the vicinity of the insertion of



Fig. 2.—*A*, a roentgenogram of the right knee which shows an island of bone in the thickened patellar ligament. There is no definite subcutaneous swelling. The diagnosis was Osgood-Schlatter's disease. *B*, a roentgenogram of the left knee which reveals calcific spicules on the anterior surface of the tibial tubercle. Note the swelling of the patellar ligament. *C*, a roentgenogram of the left knee which demonstrates an island of bone in the thickened patellar ligament. The diagnosis was Osgood-Schlatter's disease.

the patellar ligament into the tubercle and in the anterior portion of this bone. Few abnormal roentgenographic manifestations were seen in the radiotranslucent zone between the tubercle and the tibia, on the posterior surface of the tubercle and on the anterior cortex of the tibial metaphysis.

The cause is still unsettled in spite of the many reported pathologic studies.<sup>3</sup> There is good reason to believe, however, that traction of the patellar ligament has some influence on the development of this condition. Excessive or abnormal traction, such as may occur in very active boys, may produce a slow-forming proliferative lesion (calcification or ossification) at the site of the insertion of the patellar ligament. Degeneration or tearing of the patellar ligament at its insertion is probably the earliest lesion. This may be comparable to the changes leading to the production of painful swellings at the region of the insertion of the posterior tibial tendon into an accessory scaphoid.<sup>4</sup>



Fig. 3.—*A*, a roentgenogram of the left knee of a boy 14 years old which shows a large and small island of bone in the thickened patellar ligament. The diagnosis was Osgood-Schlatter's disease. *B*, a roentgenogram of the right knee in a case in which the diagnosis was Osgood-Schlatter's disease. *C*, a roentgenogram of the same knee taken six weeks after drilling of the tibial tubercle. Note especially the increase in bone formation on the anterior surface of the tubercle as well as the persistent soft tissue swelling.

3. Anardi, T.: *Chir. d. org. di movimento* **12**:187 (March) 1928. Guiliiani, G.: *ibid.* **14**:243 (Oct.) 1929; **17**:105 (June) 1932. Stracker, O.: *Ztschr. f. orthop. Chir.* **58**:242, 1932. Horbst, L.: *Arch. f. orthop. u. Unfall-Chir.* **33**:229, 1933. Block, W.: *Arch. f. klin. Chir.* **174**:172, 1933.

4. Similar pathologic changes (degeneration, fibrillation, vascularization, calcification and ossification) of the supraspinatous tendon at its insertion to the greater tuberosity of the humerus have been described.

There is clinical evidence that physical activity plays a good part in the development of the lesion, as noted by its greater frequency in boys. A higher incidence of Osgood-Schlatter's disease has been noted among the Japanese, possibly because of their habit of kneeling.<sup>5</sup> Similarly, a relative higher percentage of involvement of the tibial tubercle has been reported among the younger inhabitants of Switzerland, where mountain climbing is a fairly common sport.<sup>6</sup> It is of interest that combined lesions of Osgood-Schlatter's disease and bipartite patella have been recognized. That these may be due to traction of the patellar ligament may be surmised from the occurrence of either bipartite or high patellae in subjects with Little's disease.<sup>7</sup>

There is no definite clinical or pathologic basis on which to consider Osgood-Schlatter's disease the result of rickets, syphilis, so-called osteochondritis, infection or some disturbance of the endocrine system.<sup>8</sup> It is true, however, that in the patient with the last mentioned disease, because of obesity there may be more stress and strain on the patellar ligament which secondarily makes him more susceptible. Eight patients in our group presented Fröhlich's syndrome.

As for therapy, it seems that when operative treatment is suggested removal of the tubercle is advisable. Procedures less radical, such as drilling or bone pegging, in an attempt to fuse the epiphyseal plate between the tubercle and the tibia<sup>9</sup> may aggravate rather than relieve the pathologic condition of the patellar ligament (fig. 3B and C). It appears, however, that there is a good deal in favor of conservative

5. Asada, T., and Kato, S.: *Ztschr. f. orthop. Chir.* **48**:191 (April) 1927.

6. von Brandis, H. J.: *Ztschr. f. orthop. Chir.* **48**:239 (April) 1927.

7. Delitala, F.: *Chir. d. org. di movimento* **9**:293 (March) 1925. Ratto, O. J., and Casanovas, L. O.: *Prensa méd. argent.* **15**:106 (June 20) 1928. Serfaty, M., and Marottoli, O. R.: *ibid.* **15**:1030 (Jan. 30) 1929. Dueño, F. P.: *Rev. de cir. de Barcelona* **4**:137 (Sept.) 1932.

8. Paget, James: *Selected Essays and Addresses*, London, Longmans, Green & Co., 1902. Osgood, R. B.: *Boston M. & S. J.* **148**:114, 1903. Schlatter, C.: *Beitr. z. klin. Chir.* **38**:874, 1903; **59**:518, 1908. Jakobsthal, H.: *Deutsche Ztschr. f. Chir.* **86**:493, 1906. Alsberg, A.: *Ztschr. f. orthop. Chir.* **20**:302, 1908. Licini, C.: *Beitr. z. klin. Chir.* **78**:394, 1912. Stephens, R.: *Ann. Surg.* **73**:77 (Jan.) 1921. Graef, W.: *Beitr. z. klin. Chir.* **95**:647, 1915. Soule, R. E.: *J. Orthop. Surg.* **3**:550 (Oct.) 1921. Davis, G. G.: *Internat. Clin.* **1**:133, 1921. Rieder, W.: *Arch. f. klin. Chir.* **120**:588, 1922. Mandl, F.: *Beitr. z. klin. Chir.* **126**:707, 1922. Bader, E. R.: *Am. J. Roentgenol.* **9**:623 (Oct.) 1922. Hartley, J. N. J.: *Edinburgh M. J.* **30**:254 (Sept.) 1923. Fels, E.: *Arch. f. klin. Chir.* **129**:552, 1924. Pomeranz, M. M.: *Am. J. Surg.* **39**:17 (Feb.) 1925. Grossman, J.: *M. J. & Rec.* **121**:534 (May) 1925. Ollerenshaw, R.: *Brit. M. J.* **2**:944 (Nov. 21) 1925. Van Neck, M.: *Arch. franco-belges de chir.* **29**:119 (Feb.) 1926. Trinci, U.: *Chir. d. org. di movimento* **13**:601 (July) 1929. Gioia, T.: *Semana méd.* **2**:1857, 1929.

9. Pease, C. N.: *Am. J. Surg.* **24**:149 (April) 1934.

treatment (immobilization of the knee joint), which would relax the patellar ligament. Recurrence of symptoms about the knee in adults similar to those occurring in Osgood-Schlatter's disease may be due to an island of bone in the patellar ligament which has not united with the tibial tubercle. This is the result most likely to occur following Osgood-Schlatter's disease during childhood. In these cases, removal of the osseous island is advisable.

# CONGENITAL MEDIAN CLEFT OF THE CHIN

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Clefts of the upper lip and of the hard and soft palates are so common as to be almost routine in any large surgical clinic. Medial clefts of the chin, however, are extremely rare. No mention is made of these in most of the standard textbooks of surgery.

The case reported in this paper is one that came under the care of the State Crippled Children's Service, University Hospitals, Columbia, Mo. A child 3 days old was admitted who had a complete cleft of the lower lip and mandible extending almost down to the cricoid cartilage, with a bifid tongue as a complicating feature.

Etiologically, median clefts of the lower lip represent arrested development due to failure of union of the two inferior portions of the first branchial arch. The clefts may be simple, involving only a portion of the lip, or may extend completely down the midline to include the thorax, as is sometimes seen in cases of monster formation. The same factors which produce the usual clefts of the upper lip and palate are present in the formation of medial clefts of the lower lip and are apparently active in the early weeks of fetal life.

## REPORT OF A CASE

The child was admitted to this service on Jan. 3, 1934, when 3 days old. The extent of the deformity is shown in figure 1. The baby was apparently normal in other respects. The lip was held together with adhesive plaster during the early period in the hospital in order to facilitate feeding, and when the baby was 6 weeks old closure of the lip was done. The tongue was freed from the vermilion border and the body of the lip and the ends of the bifid mandible were then exposed subperiosteally. The lip itself was closed by undermining and freshening the edges of the cleft and approximating the two parts in the midline by the use of horsehair sutures. The edges of the lip were found to be very thin, and owing to this fact the result immediately after operation was not as good cosmetically as was desired. An attempt was made to approximate the ends of the mandible by the use of heavy chromic gut, but in passing the needle through one portion of the mandible two tooth buds were dislodged. In addition to this the child did not appear to be in very good condition, so the bone closure was left for a later date. The child recovered promptly from this procedure and was able to eat better than before operation.

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From the Department of Orthopedic Surgery, State Crippled Children's Service, University Hospitals.



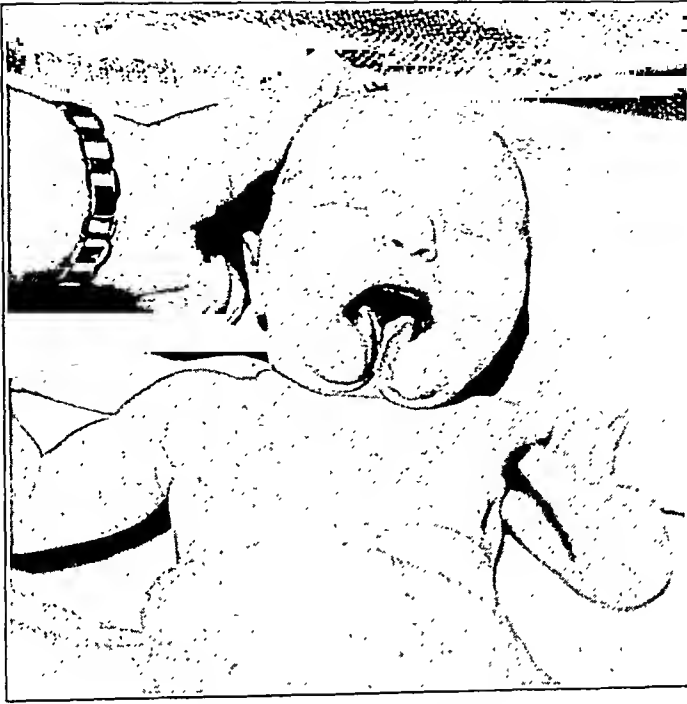


Fig. 1.—Before operation.



Fig. 2.—Nine and one-half months after closure of the defect. The mandible is still bifid. No attempt will be made to correct this until the permanent teeth erupt.

The patient was readmitted to the hospital on Oct. 17, 1934, when 10 months old, and a revision of the lip was done on October 29 with improvement of the cosmetic aspect of the lip. The chin had begun to fill out and develop. The tongue was still attached between the two portions of the mandible, and the frenum was again freed for about half an inch. Respiration and deglutition were improved following this procedure.



Fig. 3.—The scar is quite wide, and this will require a revision operation some time in the summer.

At this time it was noted that the child was subject to "blue spells" on crying, and it was found that there was a congenital lesion of the heart which had not manifested itself earlier. This lesion has been variously interpreted as a patent ductus arteriosus, patent foramen ovale or an anomaly of the tricuspid valve, but no definite decision as to the type of defect has been reached. Roentgen examination of the chest has never shown any widening of the mediastinum or other evidence of an enlarged thymus. Under anesthesia the child behaved normally, and no difficulties were experienced.

She is now 13½ months old, is able to sit erect and is attempting to stand. No teeth have erupted as yet, but her general condition is satisfactory.

Efforts to close the mandible will be delayed for several years until permanent teeth have erupted so that a suitable retention apparatus can be applied to keep a bone graft in position.

# LATE SUBCUTANEOUS RUPTURE OF THE TENDON OF THE EXTENSOR POLLICIS LONGUS MUSCLE

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Subcutaneous rupture of the tendinous segment of the extensor pollicis longus muscle as a late complication of a Colles fracture is extremely uncommon. Recently (January 1932) McMaster<sup>1</sup> found only twenty-seven such cases reported in the literature and added an additional case. Included in McMaster's contribution is the only available instance of a rupture of the tendon of the flexor pollicis longus muscle following a Colles fracture. Four cases of late rupture of the extensor pollicis longus tendon are reported by Horwitz<sup>2</sup> from Bier's clinic; two were associated with a Colles fracture, one with fracture of the base of the first metacarpal bone and one with osteitis fibrosa cystica of the styloid process of the radius.

Auxhausen expressed the opinion that rupture of this tendon is not as rare as is generally believed, since he and Hauck observed ten such cases. Platt's<sup>3</sup> experience suggested a similar point of view, for he recorded seven instances of rupture of the extensor pollicis longus tendon, six associated with fracture of the lower end of the radius and one which followed an occupational tenosynovitis. Four of the patients were operated on, and three refused to submit to surgical intervention.

The majority of the reports, most of which have been from large surgical clinics, include but one or two cases. Furthermore, complete rupture of this tendon presents a clearcut clinical picture, which is not likely to be overlooked either by the patient or by the clinician. Witness, for example, the presentation by Salzer<sup>4</sup> before the Freie Vereinigung der Chirurgen Weins in December 1933 of a man, aged 22, with spontaneous rupture of the extensor pollicis longus tendon six weeks after a fissure fracture of the radius. A favorable result was obtained by transplantation of the tendon. Oppolzer, in discussion of Salzer's report, noted that in a series of more than eight hundred fractures of the radius, he observed only two late spontaneous ruptures of the extensor pollicis longus tendon. A third case followed tendo-

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From the Daniel Baugh Institute of Anatomy of the Jefferson Medical College.

1. McMaster, P. E.: *J. Bone & Joint Surg.* **14**:93 (Jan.) 1932.
2. Horwitz, H.: *Deutsche Ztschr. f. Chir.* **234**:710, 1931.
3. Platt, H.: *Brit. M. J.* **1**:611 (April 11) 1931.
4. Salzer, A.: *Zentralbl. f. Chir.* **61**:587, 1934.

vaginitis crepitans. Good clinical results were obtained in the latter three cases by means of silk plastic sutures after the method of Lange.

A case of rupture of tendon of the long extensor muscle of the thumb is also reviewed by Lapeyre.<sup>5</sup> Operation was refused.

The reason for the rupture has been variously interpreted. Some attribute it to trauma, believing that the tendon becomes strangulated in the sheath by rupture of the tenaculum tendinum containing the nutrient blood vessels. Without nourishment the tendon degenerates, atrophies and then ruptures during some slight movement of the thumb. Others are of the opinion that it can occur only in the presence of pathologic changes in the tendon, such as tenosynovitis, tuberculosis, syphilis, previous inflammatory changes and tumors. Since no disease of the tendon can be considered as a predisposing cause in many cases, it seems reasonable to assume that some type of injury to the tendon occurred coincidentally with the fracture, culminating later in a complete rupture of the tendon.

However, one type of rupture is occasionally encountered, known as drummer's paralysis, which occurs largely as the result of some pathologic change in the tendon (occupational tenosynovitis). In some instances the rupture is complete, and in others, incomplete. The majority of the patients with this type of rupture are elderly. In thirty-nine of the fifty-one cases collected by Lapeyre the rupture was accompanied by fracture of the lower end of the radius. The fracture was often insignificant. The movement producing the rupture was often slight. The mechanism of this type of rupture of the tendon is probably best explained on the basis of attrition, analogous to a spontaneous rupture of the long tendon of the biceps muscle, which similarly occurs most commonly in elderly persons. Both of these tendons course through well developed osseous sulci, and this fixation subjects them to greater traumatism from the ordinary wear and tear. Drummer's paralysis occurs most commonly on the left side and among drummers who have been in service a long time.

Kleinschmidt stated that the experimentally produced fracture of the distal end of the radius is always associated with a coincidental transverse rupture of the sheath of this tendon, whereas the sheaths of the other tendons about the fractured radius remain intact. In many of the reported cases and in my cases, the fracture fragments were in excellent position, and no reduction of the fracture was necessary. This observation leads one to believe that factors other than the sharp end of a fracture fragment or manipulations incident to reduction are the cause of the rupture in many cases. No case of complete rupture was found reported in which the rupture occurred simultaneously with the inception of the fracture.

5. Lapeyre, J.: *Presse med.* 40:456, 1932.

A sound and tenable explanation of the mechanism of this injury to the tendon is best obtained by an analysis from the morphologic point of view. Three factors deserve consideration: (1) the anatomic variations in the groove of this tendon on the distal dorsal surface of the radius, (2) the anatomic course of the tendon and (3) the blood supply of the tendon. In order to ascertain the variations in the grooves on the dorsal surface of the distal end of the radius more than three hundred radii were studied. While there is a definite suggestion that certain types of formations exist, many minor variations are encountered that do not lend themselves readily to inclusion in groups. One fact stands out prominently, i. e., that the groove for the extensor pollicis longus tendon is the most prominent of the osseous sulci or incisurae on the dorsal surface of the distal segment of the radius (fig.).

The groove for the extensor pollicis longus tendon is narrow and oblique, and it is frequently bordered by well marked ridges. The incisurae for the other extensor tendons are somewhat broad and shallow. Considerable variation is present in the bony ridges bounding the sulcus of the extensor pollicis longus tendon (see fig.). The ridges and the groove give origin to strong fibers which strengthen the dorsal (posterior) radiocarpal ligament. The latter serves as an additional factor to fix this tendon in its narrow and oblique sulcus. Tracing the anatomic course of the tendon, it is to be recalled that on emerging from its osteofibrous groove beneath the posterior or dorsal radiocarpal ligament it passes obliquely across the dorsal surfaces of the carpus and over the tendons of the radial extensor muscles to gain insertion into the base of the second phalanx.

The unique anatomic course and the fixation of this tendon would appear to be important factors in the genesis of a rupture of the tendon and of the accompanying blood vessels. The importance of the anatomic fixation of blood vessels as one of the contributing factors in the causation of vascular injuries following a severe contusing violence has been commented on in a previous communication.<sup>6</sup>

That there is a scanty vascular supply of tendon tissue, particularly of segments that traverse osteofibrous channels, is well known. The repair of an injury to a tendon depends on the proliferation of tissue from several sources, most of the new tissue coming from the sheath and the surrounding connective tissue and the external peritoneum establishing vascular connections with the surrounding tissues. When an injury occurs in the part of a tendon occupying an osteofibrous sulcus repair takes place with great difficulty because of the absence of adequate surrounding tissues. The blood vessels supplying the tendon

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6. Lipshutz, B.: Surg., Gynec. & Obst. 46:62 (Jan.) 1928.

are for most part disposed longitudinally and traverse the areolar tissue which separates and surrounds the tendon bundles.

In the two cases here recorded the clinical picture of rupture of the tendon of the long extensor muscle of the thumb did not appear until five and six weeks, respectively, had elapsed after the occurrence of



Seven types of sulci for the tendon of the extensor pollicis longus muscle.

the fracture of the radius. Both of the fractures were in good position, and no manipulations were necessary for their reduction. Thus the only tenable explanation for the subsequent rupture of the tendon was an initial injury to the blood vessels of the tendon and the later development of necrosis of the tendon, owing to the failure of the surrounding vessels to establish a collateral circulation adequate for repair.

In a number of studies on the variations of the vascular tree, it is noteworthy that definite hypogenesis of the blood vessels is present in approximately from 5 to 8 per cent of all cadavers. Such hypogenesis consists of definite, smaller-calibered blood vessels and a decrease in the number of branches. The microscopic image confirms the latter findings, for the examination of a considerable number of arterial walls shows a wide variation in the general mural structure. The elastic content and the muscle content exhibit wide variations. In some instances the vessel wall, because of its tenuous mural structure, appears fragile; in other cases the vessels are strong and robust. These vascular variations are recorded independent of age and disease and represent distinct morphologic types. Conversely considered, the presence of additional branches and accessory arteries is not uncommon in the experience of any observant anatomist. That the structure of the arterial wall and the type of person are significant factors in the genesis of this injury appears to be supported by the following data: Twenty-two of thirty-two collected cases occurred in women. Of the two cases that I observed, one was in a woman, aged 22, who was somewhat undernourished, and the other, in a man of the type who usually shows arterial hypogenesis. The greater incidence of injury to this tendon in women may have its basis in a more frail structure of their vessel walls. In addition, the skeleton of women in general is characterized by the smaller development of processes and ridges for muscular attachment and weaker ligamentous structures, offering less protection to the contained tendon and its accompanying vessels.

#### REPORT OF CASES

CASE 1.—A girl aged 19 had a fracture of the lower end of the left radius, with very little displacement. Five weeks later, she felt something snap while wrapping a package and noticed that the distal joint of the thumb was hanging at an angle and could not be extended. She refused to submit to surgical intervention.

CASE 2.—A man aged 26 had a fracture of the lower end of the right radius. A roentgenogram showed the fracture to be in excellent position. Six weeks after the fracture the patient noticed that the distal joint of the thumb was hanging at an angle of 140 degrees and could not be extended, indicating late rupture of the tendon of the extensor pollicis longus muscle. He did not hear or feel any tear and could assign no reason for the disability. At no time did he complain of pain. Four months after the fracture he was referred to me by his physician; he presented the typical picture of late rupture of the tendon of the pollicis longus muscle. At operation a longitudinal incision was made on the dorsal surface of the right wrist. The somewhat frayed glistening distal end of the ruptured tendon was located immediately distal to the caudal border of the dorsal radiocarpal ligament. As the course of the tendon was followed proximally, its sheath was found occupied by a frayed, grayish, thin, friable strand, extending to its muscular portion, indicating complete degeneration of the tendon from a point

immediately distal to the border of the dorsal radiocarpal ligament to its muscular portion. The destroyed part of the tendon was resected, since end-to-end approximation was impossible even with marked dorsiflexion. Because of the absence of any tendinous fibers in its proximal segment, the distal segment of the tendon was sutured to the extensor pollicis brevis muscle. The part was immobilized for three weeks. The result was good and the wound healed by first intention. There are now active movement of the distal phalanx to 110 degrees and active stretching in abduction and extension to 175 degrees. There is some thickening at the point of transplantation.

#### TREATMENT

Repair by operation should be undertaken without delay. In cases of recent rupture the lesion can be repaired by direct suture, for degeneration of the tendon develops slowly. The studies of Mason and Shearon<sup>7</sup> showed that the tendon itself takes an important part in healing. Because of its scanty blood supply and the nature of tendon tissue, the repair progresses slowly. This tardiness of response in the tendon is compensated by an early response of the sheath. In suturing the ends of the tendon the point of attachment of the suture should be 1 cm. or more from the end of the stump so as to leave the latter untraumatized. It should be tied so that the knot does not lie between the ends of the tendon. Similarly the sheath should be disturbed as little as possible. It may be wise, as suggested by Mason and Shearon in their studies on repair of tendons, in performing end-to-end suture of a tendon in instances in which tension is considerable to put in a small segment of tendon graft. Many surgeons have advocated the use of fascia or other connective tissues for tendon grafts. The experimental studies of Mason and Shearon, however, indicated that a defect in a tendon should be filled with a tendon graft plus its sheath tissues and not with fascia, since the tendon forms true tendon which will not stretch as would ordinary connective tissue. Silk is the preferable material for sutures. In a number of the reported cases, silk plastic sutures inserted by the method of Lange gave very satisfactory results. If possible, the oblique course of the tendon should be preserved. But it is probably better not to use the original groove for the following reasons: 1. The inadequate surrounding tissue may interfere with repair. The connective tissues surrounding the tendon are of the greatest importance in the repair of a wound in a tendon. They convey blood vessels and lymphatic vessels to it and permit easy gliding of the tendon. 2. The presence of scarring and adhesions may make the groove unsuitable. The construction of a pulley by means of fascia lata, as recommended by Platt, may be used successfully to overcome the latter difficulty.

7. Mason, M. L., and Shearon, C. G.: The Process of Tendon Repair, *Arch. Surg.* 25:615 (Oct.) 1932.



As an alternate method, when the entire proximal portion of the tendinous segment is destroyed the distal end of the tendon is attached to the extensor pollicis brevis muscle, as was done in case 2. This method prevents dropping of the thumb, but it cannot restore independent action of the long extensor muscle. The thumb is supported in extension for three weeks after any method of repair. Movement may be started cautiously from the sixth or seventh day, but no force should be exerted before the third week. Faradic stimulation of the muscle belly in the forearm can be used from the seventh day on.

# INTRACRANIAL PRESSURE IN HEAD INJURIES

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Within recent years there has been a notable increase in what for lack of a better term have been classed simply as "head injuries." Although the term does not so specifically indicate, "head injury" has come to be synonymous with "brain injury." It has been assumed that cerebral trauma sufficient to cause subjective symptoms or to exhibit objective signs would be attended by the usual phenomena of injury elsewhere, viz., edema, hemorrhage and gross structural damage, and that occurring within a closed container such as the skull it would have as its most constant and formidable phenomenon increased intracranial pressure.<sup>1</sup> It is on this assumption that most of the accepted treatment of craniocerebral trauma is based. It is assumed that the most common occurrence following brain trauma is cerebral edema and that this is one of the prominent factors causing death from such injuries.<sup>2</sup> In accordance with this belief spinal drainage is resorted to as a routine procedure by many, and this is often supplemented by the use of hypertonic solutions administered intravenously or by mouth or bowel.<sup>3</sup> As a logical addition Fay<sup>4</sup> has advocated rigid restriction of fluid intake. All of these measures are directed toward the reduction of intracranial pressure. As a result of the stress laid on these measures the belief has become widespread that increased intracranial pressure is a common if not constant accompaniment to severe head injury. It has been my good fortune to have under observation for the past three or four years at the Minneapolis General Hospital between 300 and 400 cases of head injury each year. In attempting to analyze this material and to rationalize the treatment my associates and I have engaged in a rather exten-

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From the University of Minnesota and the Minneapolis General Hospital.

1. (a) Peet, M.: Symptoms, Diagnosis and Treatment of Acute Cranial and Intracranial Injuries, New York State J. Med. 29: 558, 1928. (b) McClure, R. D., and Crawford, A. S.: Management of Craniocerebral Injuries, Arch. Surg. 16: 459 (Feb.) 1928. (c) Jackson, H.: Management of Acute Cranial Injuries, Surg., Gynec. & Obst. 34: 494 (April) 1922. (d) Stewart, W. H., and Luckett, W. H.: Skull Fractures, Am. J. Roentgenol. 6: 481, 1925.

2. (a) Dandy, W. E.: Acute Head Injuries, in Lewis, D.: Practice of Surgery, Hagerstown, Md., W. F. Prior Company, Inc., 1932, vol. 12, chap. 1, p. 265. (b) Sachs, E.: Diagnosis and Treatment of Head Injuries, J. A. M. A. 81: 2159 (Dec. 29) 1923.

3. Sachs.<sup>2b</sup> McClure and Crawford.<sup>1b</sup>

4. Fay, T.: Head Injuries, J. Iowa M. Soc. 20: 447, 1930.

sive study of all the factors involved. In reviewing the evidence presented by lumbar puncture it has been of interest to note how infrequent are the findings of abnormal intracranial pressure. This observation resulting from the routine examination of a number of records gave rise to the question of how frequently increased intracranial pressure is associated with cerebral trauma and what its relation to the cerebral symptoms is. The following discussion is an attempt to answer this query.

Much of the difficulty arising out of the study of cerebral trauma lies in the classification of the material studied. Some of it appears under the heading of concussion, some of it under the heading of skull fracture, some of it under that of the gross or the histopathologic observations at autopsy, and some under the broad general term of craniocerebral trauma. It is needless to say that such variation in classification is bound to result in considerable variation in findings. A comprehensive and entirely satisfactory classification would be, perhaps, too involved and unwieldy by reason of the many necessary qualifications, and an attempt has been made here to compromise the difficulties by grouping the material under one symptom which is common to all cases and is easily measured. Inasmuch as the most constant and most specific evidence of brain dysfunction is the loss of consciousness it has been taken as the criterion for the basis of classification in this series. To avoid the inclusion of trivial injuries and injuries with only slight evidence of cerebral damage the minimal limit of unconsciousness has been arbitrarily placed at one hour.

#### MATERIAL AND METHOD OF STUDY

The series comprises 128 cases of head injury with periods of unconsciousness extending from one hour to several days. These cases have been carefully studied with regard to the following data: age, sex, period of unconsciousness, subjective complaints, neurologic findings, clinical behavior, results of roentgen and laboratory examinations and spinal fluid pressures. In each of the cases a careful record was kept of the state of consciousness. Care was taken to differentiate between stupor, aphasia and the irrational conscious state. The period of complete unconsciousness was noted, and during this time the blood pressure was recorded at thirty minute intervals, likewise the pulse rate, temperature and respiratory rate. Following the return of consciousness these observations were recorded hourly until the patient became symptom-free. In each instance as careful a physical examination was made as the patient's condition would permit directly on his admission to the hospital and was repeated at daily intervals. Examination of the neuromuscular mechanism was made, and the skin and tendon reflexes were recorded; also, careful examination was made of the eye with regard to the pupillary reflexes and the extra-ocular movements. Ophthalmoscopic examination was made at about the fourth or sixth day following injury. As the series contained no case suggestive of brain tumor, and as no evidence of spinal fluid block could be demonstrated, a direct estimate of intracranial pressure was made in terms of spinal fluid pressure obtained by puncture in the second or third lumbar interspace. With the patient in the horizontal position and lying

on his side, lumbar puncture was performed on the second day and as frequently thereafter as conditions warranted. In performing lumbar puncture the needle was connected directly to a water monometer of 1 mm. caliber, and no fluid was allowed to escape before taking the reading. In order that the figures thus obtained might be compared with readings made in millimeters of mercury it was necessary to correct for capillarity of the instrument. On repeated observation this was fixed at 15 mm. After the pressure reading had been obtained, a few centimeters of fluid was examined for the presence of blood. Only those cases in which gross blood could be identified in the cerebrospinal fluid were classed as positive for blood. In no instance in this series was any attempt made to affect the intracranial pressure by spinal drainage, the use of hypotonic solutions or restriction of fluid intake. In addition to the foregoing record, post-mortem examination of the brain was made in each of the fatal cases and the observations appended.

#### ANALYSIS OF DATA

From the assembled individual records the data were collected and catalogued as follows: When the cases were grouped according to patients' ages the greatest number fell within the 20 to 25 year period: the frequency fell off gradually as old age approached, but there were secondary peaks at 35 and 45 years. This curve of distribution (chart 1) probably signifies that the greatest exposure to head injuries occurs in early adult life and that exposure to such injuries gradually decreases as the person's activities decrease. It is also probable that the secondary peaks of the curve indicate the time of life when the person's activities are still unrestricted but when his neuromuscular mechanism is showing the first signs of age, of which he is unaware and by reason of which he is less able to avoid injury than in early adult life. As he grows older his exposure to injury is limited, he also exhibits a greater degree of caution, and the curve falls away rather sharply.

In the 128 cases there were 20 deaths, representing a mortality of 15.6 per cent, distributed over the age periods designated in chart 2. The greatest number of deaths fell within the 55 to 60 year period. As persons in this period were not subject to injuries of greater severity than those occurring in youth it may be supposed that the older person is less able to survive an injury to the brain than the young one.

The distribution of intracranial pressures over the whole series is represented in chart 3. It will be noted that by far the greatest number of cases are grouped under the 125 mm. level. From this point the curve drops abruptly to the 200 mm. level, and from here, with the exception of a moderate rise at the 225 mm. level, it flattens out to continue in an almost straight line to the 500 mm. mark. The final pressure reading of the curve indicates not 500 mm. alone but 500 mm. or over. In considering these figures and those which follow some thought must be given the term "normal." As Ayer<sup>5</sup> stated, "The normal spinal

5. Ayer, J. B.: Cerebrospinal Fluid Pressure, in Dana, C. L., et al.: Cerebrospinal Fluid, New York, Paul B. Hoeber, Inc., 1926, p. 160.

fluid pressure may be anything," and this statement seems true in view of the wide limits of variation recorded by various observers. Barré and Schrapf<sup>6</sup> on the basis of 310 observations concluded that the normal limits of variation of spinal fluid pressure lie between 50 and 200 mm. of water. Ayer placed the figures at 100 to 200 mm., stating that any reading above 250 and 300 mm. is distinctly abnormal. Weigeldt<sup>7</sup>

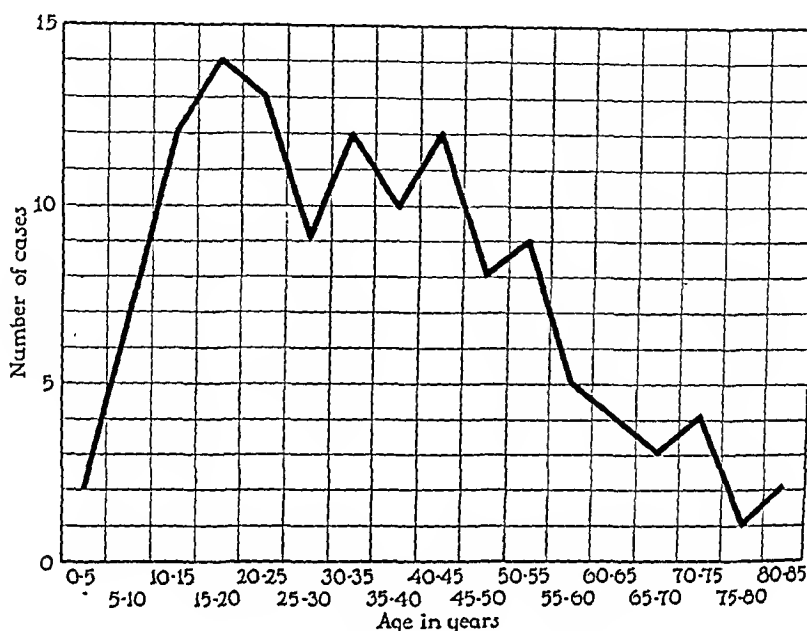


Chart 1.—Incidence of head injuries according to age.

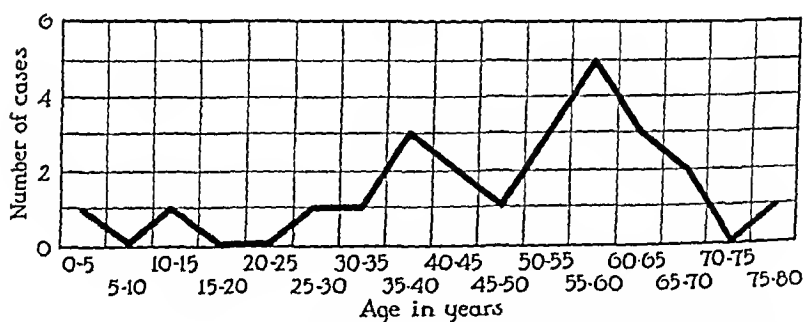


Chart 2.—Incidence of mortality in head injuries according to age.

determined a much narrower range of variation, placing the figures at 150 to 170 mm. He also stated that a pressure over 300 mm. is distinctly abnormal. Dreyfuss and Becker<sup>8</sup> established the upper limit of

6. Barré, J.-A., and Schrapf, R.: *Sur la pression du liquide céphalo-rachidien*, Bull. méd., Paris **35**: 63, 1921.

7. Weigeldt, R. W.: *Studien zur Physiologie und Pathologie des Liquor Cerebro-Spinalis*, Jena, Gustav Fischer, 1923, p. 150.

8. Dreyfuss and Becker, quoted by Ayer.<sup>5</sup>

normal at 200 to 220 mm.; Key and Retzius,<sup>9</sup> at 160 to 200 mm., and Cottin and Saloz,<sup>10</sup> at 200 to 300 mm. These are but a few of the conclusions of many workers, but they probably represent a reasonably accurate estimate. For the purposes of this study it was necessary to establish an upper limit of normal spinal fluid pressure and this has been placed at 180 mm. as this figure appears to be well within the upper limits of normal as determined by the majority of observers. As previously stated, cerebrospinal fluid pressure has been taken as a measure of the intracranial pressure, and to avoid confusion the latter term will be used in the comment which follows. Of the 128 cases studied 21, or 16.4 per cent, exhibited intracranial pressures above 180 mm. In

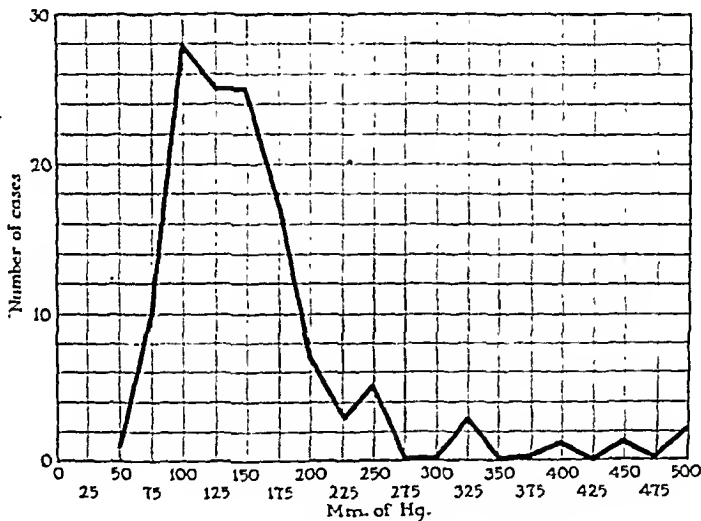


Chart 3.—Intracranial pressure in head injuries.

only 7 of these, or 5.4 per cent, was the pressure in excess of 300 mm., as may be noted in the curve of distribution in chart 3. While the latter figures denote distinctly abnormal pressures, it is worthy of note that 5 per cent is a remarkably small part of the total.

Of the total number of patients 41 sustained fractures of the skull as demonstrated by roentgen examination and 87 were classed as having no skull fractures. No apparent relationship could be established between skull fracture and severity of brain injury. As evidence of the severity of brain damage or injury, the cases were again classified according to periods of unconsciousness. This is shown in chart 4. The greatest

9. Key, E. A. H., and Retzius, G.: Studien in der Anatomie des Nervensystems und des Bindegewebes, Stockholm, Samson & Wallin, 1875-1876.

10. Cottin and Saloz: La mesure de la pression du liquide céphalo-rachidien. Rev. de méd., Paris 35: 511, 1916.

number of cases is seen to fall within the one to five hour period. From this point to the ten hour period the number of cases decreases rapidly to reach a minimum at the twenty-five hour period only to rise again at the forty-five hour period. As previously mentioned, this curve of distribution cannot be correlated with that of skull fracture. The spinal fluid removed after reading the pressure was found to be bloody in 73 cases, or 57 per cent. Vomiting was observed in 60 cases, or 46.9 per cent. Examination of the clinical record relative to pulse rate and blood pressure revealed only slight and insignificant variations. In only 1 case did the rise in blood pressure and the fall in pulse rate occur as described by Cushing.<sup>11</sup> It was noted that in the terminal state the

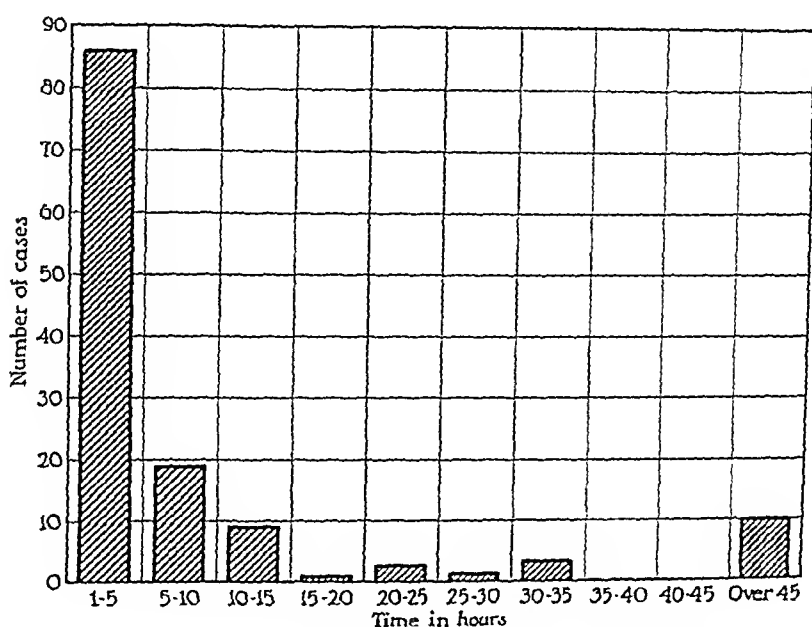


Chart 4.—Period of unconsciousness in head injuries.

pulse became rapid and the blood pressure fell, but this circumstance was not uniformly related to intracranial pressure.

Again, classifying the cases on the basis of intracranial pressures of 180 mm. or more, the clinical data were reassembled and correlated with the two groups of normal and abnormal pressure to determine whether or not the presence or absence of abnormal intracranial pressure could be determined and its intensity measured by the various clinical phenomena observed. It was found by comparing the two curves as in chart 5 that the age incidence and the incidence of abnormal intracranial pressure were in no way related. That is to say, the response of the young person is proportionately the same as that of the older person in terms of intracranial pressure. Likewise it was found that

11. Cushing, H.: Blood Pressure During Cerebral Compression, *Bull. Johns Hopkins Hosp.* 12: 290, 1901.

no causal relationship obtained between the periods of unconsciousness and the accompanying intracranial pressures, as may be determined by examining chart 6. It will be noted that the percentage of patients having abnormal intracranial pressure is quite as high in the group having a period of unconsciousness of one hour as in those having a period of unconsciousness of forty-five hours or more. The relation of intracranial pressure to skull fracture is equally inconclusive. Of the 41 patients exhibiting fractures of the skull 9, or 21.9 per cent.

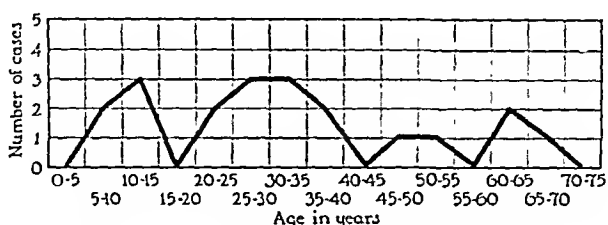


Chart 5.—Incidence of abnormal intracranial pressure according to age.

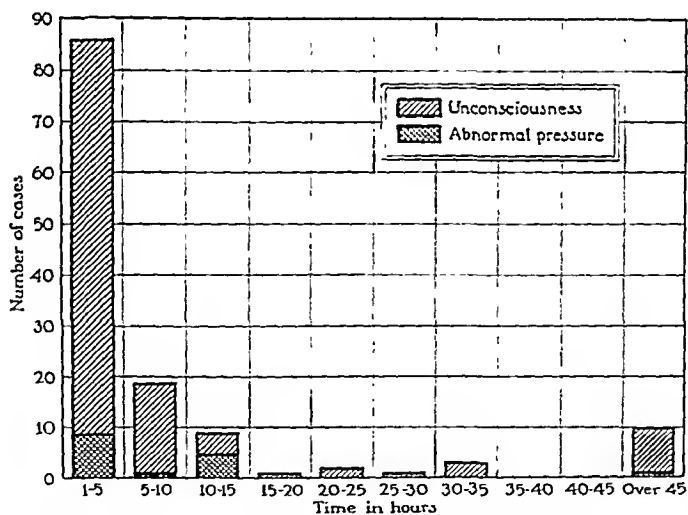


Chart 6.—Relation of period of unconsciousness to period of abnormal intracranial pressure.

exhibited intracranial pressure of more than 180 mm. and of the remaining 87 patients in whom no skull fracture could be proved 10, or 11.5 per cent, exhibited abnormal intracranial pressure. It appears from this that abnormal intracranial pressure is definitely more frequent in patients having fracture of the skull, but examination of the curve of distribution of the individual cases as seen in chart 7 leads to the belief that some other more important factor is the determining cause. This is further substantiated by the observation that of the 41 patients with skull fractures 34, or 82.9 per cent, exhibited gross blood in the spinal fluid and



of the 87 in which no skull fracture was shown only 22, or 25.2 per cent, exhibited bloody spinal fluid. Of the total number of patients studied 56, or 43.7 per cent, exhibited gross blood in the spinal fluid. This in itself is of little importance until it is correlated with abnormal intracranial pressure; in all patients having abnormal intracranial pressure a bloody spinal fluid was found. This finding appears to indicate a direct relationship between hemorrhage and intracranial pressure. In close agreement with this observation are the observations at autopsy. Of the 20 patients who died 7, or 35 per cent, had an intracranial pressure of more than 180 mm. and, of these, 6 had extensive subdural hemorrhage while 1 presented extradural hemorrhage.

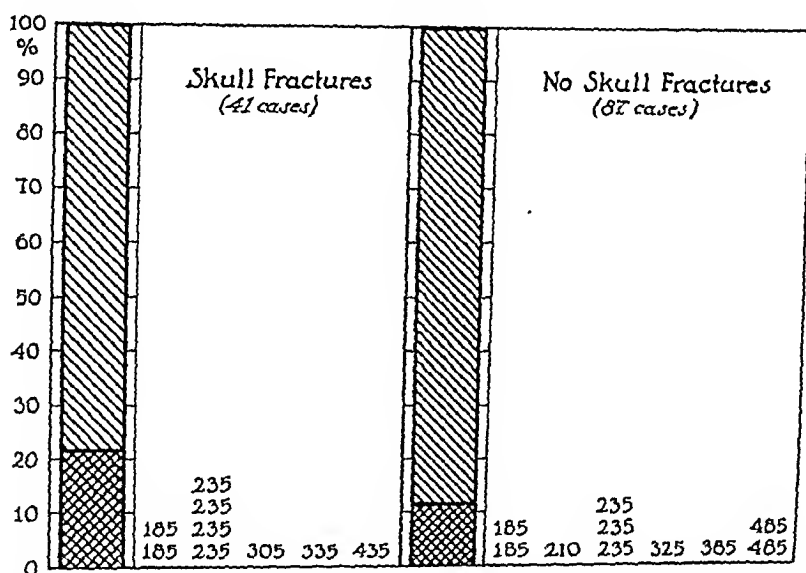


Chart 7.—Relation of abnormal intracranial pressure (cross-hatching) to skull fracture (diagonal stripes).

Further study of the autopsy material is interesting. It will be noted in table 1 that the patients having intracranial pressure of more than 180 mm. fall into two groups: those who survived and those who died. Of the first there were 14 and of the second 7. It will be noted that in those surviving the intracranial pressures show substantially the same distribution as in those who died and that the extremes of intracranial pressure appear in both groups. Also in examining table 2, in which the 20 patients who died are grouped again into two groups, one having pressures over 180 mm. and the other pressures under 180 mm., it will be seen that the majority of these patients died with relatively low intracranial pressures. From the evidence of these two tables it may surely be said that in view of the fact that two thirds of the patients died with normal intracranial pressure and that of the group having abnormal intracranial pressure, those surviving had pressures comparable to those who died there is no definite or causal relationship between intracranial

pressure and death. That is to say, that by no means is a fatal outcome to be expected in cases of head injury with abnormal intracranial pressure, and as a corollary it might be stated that the determining factor in death is not the degree of intracranial pressure which may exist but whether or not it affects a vital center.

Thus far mention has been made only of hemorrhage as bearing any relation to abnormal intracranial pressure. The evidence in all cases examined post mortem tends to support this relationship inasmuch as in no instance was any evidence of cerebral edema found. In no instance was the dura tense except as a result of hemorrhage, and in no instance was there any demonstrable amount of subarachnoid fluid. The cause of death in head injury is by no means clear, and although it is

TABLE 1.—*Abnormal Intracranial Pressures of Patients Who Survived and of Patients Who Died*

Survived (14 Patients)								Died (7 Patients)					
185				235				235					
185			225	235				235					
185	200	210	225	235	305	310	385	500	100	235	325	430	500

TABLE 2.—*Distribution of Intracranial Pressures Over and Under 180 Mm. in Patients Who Died*

Pressures Over 180 Mm. (7 Patients)						Pressures Under 180 Mm. (13 Patients)							
	225						100				155		
	235						100				135		155
190	235	325	430	500		75	80	100	105	110	135	135	165

in effect the result of disturbance in the medullary portion of the brain, and Dandy suggests it may be due to localized pressure, it certainly is not, in the light of the figures given in a foregoing paragraph, the result of generalized abnormal intracranial pressure in the majority of instances. As regards the clinical data, correlation with abnormal intracranial pressure is difficult and inconclusive except for the negative findings. Examination of the eyes as to pupillary change and extra-ocular muscular dysfunction reveals little of value. Of the patients having abnormal intracranial pressure only 6, or 31.5 per cent, showed eye changes. As these changes occurred in 13.7 per cent of the patients with normal intracranial pressure they could not be taken as indicative of the presence or of the degree of abnormal pressure. As might be expected, papillary edema was rather rare. It was of course absent in all cases in which the intracranial pressure was normal and present in only 4 of the 21 cases in which the pressure was abnormal. This low figure is probably due more to the lack of time for development than to the

degree of abnormal pressure. The findings with regard to the cardiovascular phenomena were of interest particularly in the light of a generally accepted view of their importance. In only 1 case was the onset of intracranial pressure signalized by a fall of pulse rate and a rise of blood pressure. Even in the fatal cases, although death was immediately preceded by a rise in pulse rate and a fall in blood pressure, the same circumstance was noted in fatal cases without increase in intracranial pressure. Observations with regard to vomiting were interesting because this, too, has been commonly identified with increase of intracranial pressure.<sup>2a</sup> In view of the experience of many observers regarding intracranial pressure in cases of brain tumor there can be no question but that vomiting is an almost constant symptom of high intracranial pressure exerted over some period of time. This, however, does not appear to be true in cases of acute head injury. Of all the patients in the series 60 vomited. Of the 21 patients with pressure of 180 mm. or more, 9, or 42.8 per cent, vomited, and of the 107 remaining patients 51, or 47.6 per cent, vomited. From these figures it appears that the occurrence of vomiting is in itself neither an evidence of increased intracranial pressure nor a measure of its degree.

#### CONCLUSIONS

Assuming that the foregoing data are accurate and sufficiently extensive to be of statistical value, it appears that the following conclusions are reasonable: 1. In cases of severe head injury abnormal intracranial pressure is not a frequent occurrence, and only in a small percentage of the cases will it exceed 300 mm. 2. Abnormal intracranial pressure is not a frequent finding in the fatal cases nor is it a frequent cause of death. 3. Unconsciousness is not in itself evidence of abnormal intracranial pressure nor is the period of unconsciousness a measure of the degree of intracranial pressure. 4. Unless abnormal intracranial pressure develops rapidly and is of sufficient degree to approximate the blood pressure, changes in pulse rate and blood pressure do not develop, and such changes cannot be considered as satisfactory evidence of abnormal intracranial pressure. 5. Neurologic findings, such as ocular reflex change and reflex changes elsewhere, are not signs of increasing intracranial pressure. 6. Increased intracranial pressure is almost invariably attended by blood in the spinal fluid. 7. When abnormal intracranial pressure occurs it is the result of hemorrhage, extradural, subdural or within the substance of the brain. 8. It is not probable that abnormal intracranial pressure of a degree sufficient to endanger life is susceptible to treatment by spinal drainage or by the use of hypertonic solutions. It also appears reasonable that such few abnormal intracranial pressures as occur which are of sufficient degree to endanger life are best treated surgically.

## FIFTY-EIGHTH REPORT OF PROGRESS IN ORTHOPEDIC SURGERY

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### CONGENITAL ABNORMALITIES

*Congenital Coxa Vara.*—In a general discussion of congenital coxa vara, Roederer<sup>1</sup> states that two conditions quite different in their etiology and their course can be differentiated. The early rachitic coxa vara has a very deformed head and marked osteoporosis with a wide oblique epiphyseal line, while congenital coxa vara shows an intact femoral head with normal osseous density and a normal epiphyseal line almost vertical in direction. In congenital coxa vara deformities of the head come slowly with use. Often the lesion is unilateral. The deformity is one of faulty development of the femoral neck; there may be shortness of the femoral neck, or the upper portion only may develop into a hooked process, or the neck may not develop at all. Many persons with coxa vara are able to lead a fairly normal existence, but later arthritis develops with increased density of the head. Treatment with repeated application of plaster casts even in small children has been unsuccessful, and surgical intervention, usually osteotomy, has been necessary. In adults abduction and extension in a plaster cast with a subtrochanteric osteotomy are most helpful.

*Physiologic Treatment of Congenital Dislocation of the Hip.*—Stewart<sup>2</sup> formulates the principles of treatment on the basis of embryo-

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This report of progress is compiled from a review of 207 articles selected from 297 titles appearing in medical literature approximately between Feb. 22, 1935, and July 1, 1935. Only those which show progress were chosen for review.

1. Roederer, C.: Bull. Soc. belge d'orthop. 7:109, 1935.

2. Stewart, S. F.: J. Bone & Joint Surg. 17:11, 1935.

logic and phylogenetic study and strives to show the possibility of obtaining the necessary preoperative information by examination of x-ray films. Three great lessons are to be learned: (a) The degree of antetorsion and the extent of ischial defect are reciprocal factors. (b) It is not the defective iliac portion of the acetabulum which causes dislocation when the hip is adducted after conjugation, but rather the folding up of the inferior capsule, which acts as a lever to lift the hip out of the socket. (c) In most, if not all, hips treated by closed reduction, the femoral head erodes its way through the infolded capsule before it becomes completely conjugated; otherwise it would be dislocated as it is brought into adduction. The original article should be read in order to comprehend the author's meaning, but the final sentences may be given here without comment: "We 'resign to the secular Arm' the pumphandling manipulators and users of racks. We would, however, emphasize the value of marginal additions to the acetabular bearings and we have pointed out the way for their proper localization. In the hips which have retained the reptilian form it would seem that a refined bifurcation operation would be desirable."

*Comparative Analysis of the Results of Open and Closed Reductions in Congenital Dislocation of the Hip.*—Kidner<sup>3</sup> gives a candid comparison of the results in 26 cases in which 34 luxations were reduced by open operation and 13 cases in which 22 luxations were reduced by the closed method. The original paper deserves reading, and only the final conclusions are given here: 1. The results of closed reduction, even in young children, are often unsatisfactory, although the only perfect end-result from the clinical and roentgenographic standpoints falls in this group. 2. Force should never be used to obtain reduction. 3. Except in rare cases, the anatomic changes inherent in congenital dislocation require open surgical treatment if reduction is to be intelligently performed and permanently satisfactory. 4. The results of open reduction are better than those of closed. 5. Open reduction is not dangerous. 6. A small incision which does little damage to soft parts or muscle attachments is sufficient. 7. Adhesion of the capsule to the side of the ilium is the major factor in preventing reduction. 8. The period of immobilization in plaster is much shorter after open than after closed reduction.

*Open Reduction in Congenital Dislocation of the Hip.*—Farrell and Howorth<sup>4</sup> summarize the results in a series of 492 cases in which treatment was by the closed method, in 42 per cent of which the method was successful. In a series of 122 cases, successful open reductions were obtained in 77 per cent. "Good functional results were secured

3. Kidner, F. C.: *J. Bone & Joint Surg.* **17**:25, 1935.

4. Farrell, B. P., and Howorth, M. B.: *J. Bone & Joint Surg.* **17**:35, 1935.

in 78 per cent of the open reductions." They conclude that closed manipulation is the method of choice during the first year of life and may be attempted up to 3 years of age. The shelf stabilization is the most satisfactory operation for most children over 6 years of age. Traction with adhesive plaster is of little or no value before reduction; after reduction it may be useful when there is tension at the hip. The chief factors in redislocation are the size and shape of the acetabulum and the redundancy of the capsule. When the capsule is adherent it should be freed superiorly, a sufficient section removed, and an anatomic closure secured. Anteversion favors redislocation and should be corrected when such is the case. The principal causes of postoperative limitation of motion which can be avoided are tension of the tissues about the hip joint, damage at the superior acetabular margin and the presence of a large area of raw bone or raw soft tissue. Coxa plana is due to a circulatory disturbance caused by tension on the capsule and adjacent tissues and is almost wholly avoidable.

*Painful Congenital Subluxation of the Hip.*—Five women ranging in age from 29 to 46 years were operated on by Owre<sup>5</sup> for the relief of pain from congenital dislocation of the hip. The method of Lance was used. A plate of bone from 2 to 3 mm. thick and from 2 to 3 cm. wide was turned down from the ilium over the femoral head and fastened to the articular capsule with catgut. A long tibial graft was broken and laid over this bone plate like roof-tiling, with the periosteum downward. If abduction at the hip was less than 45 degrees a subtrochanteric osteotomy was also performed. A plaster cast with the hip in extreme abduction was worn until healing had taken place. The author mentions that after operation these patients were free from pain on walking.

*Coxa Magna.*—Ferguson and Howorth<sup>6</sup> report a group of cases under the term "coxa magna"—a condition in which there is enlargement of the femoral head and neck due to local disturbances of circulation. In 13 cases the symptoms and signs of coxa plana were presented without the abnormalities of bone or cartilage characteristic of coxa plana or slipping of the upper femoral epiphysis. The cause in each case was apparently a disturbance of circulation in the femoral head produced by sclerotic changes in the soft tissues about the femoral neck following subacute arthritis probably infectious in origin. For such a condition they advise treatment by rest in bed without immobilization and the removal of foci of infection. They believe coxa magna

5. Owre, A.: Acta chir. Scandinav. 76:369, 1935.

6. Ferguson, A. B., and Howorth, M. B.: Coxa Magna: A Condition of the Hip Related to Coxa Plana, J. A. M. A. 104:808 (March 9) 1935.

to be due to the same pathologic conditions producing coxa plana, but less severe. The article is illustrated by roentgenograms and photomicrographs of specimens.

#### DISTURBANCES IN MINERAL METABOLISM

*Mineral Metabolism in Osteogenesis Imperfecta.*—Swanson and Iob<sup>7</sup> report studies of the mineral metabolism in a case of osteogenesis imperfecta. Viosterol, 30 drops daily, was given with apparent improvement in the retention of calcium and phosphorus. Poor retention of sodium was the most striking observation. An analysis of bone showed a low total ash content but did not confirm the high values reported for magnesium, sodium and potassium. A review of the findings in other cases reported in medical literature is given.

*Calcium and Phosphorus Metabolism in Osteomalacia.*—The response of 4 patients suffering from osteomalacia was studied by Liu and his collaborators.<sup>8</sup> Briefly, the authors found that although the abnormal conservation of calcium because of lack of vitamin D is identical in all cases of osteomalacia, two types are recognizable by the serum calcium and serum phosphorus levels; in one the calcium is low and the inorganic phosphorus is normal; in the other, this is reversed. In the former tetany and lenticular opacities are present; in the latter bone tenderness and skeletal deformities are more common. Decalcification may be mild in the former and advanced in the latter. Both types respond to vitamin D therapy. Serum inorganic phosphorus when low rises rather slowly, being susceptible to the influence of factors other than vitamin D. It is not known whether or not the state of the parathyroid glands exerts some controlling influence.

*Conception of Osteomalacia and Its Importance to China.*—Maxwell<sup>9</sup> states that the name "osteomalacia" should be replaced by the term "adult rickets," for it is a sign which may appear in a number of disorders. This disease, caused partly by actual shortage of calcium and phosphorus combined with a lack of vitamin D, has as its main symptoms pain in the back and thighs and softening of the bones of the pelvis, chest, long bones and vertebrae. It has to be distinguished from osteomalacia due to: (1) hyperparathyroidism, (2) hyperthyroidism, (3) steatorrhea, (4) renal rickets, (5) diabetes and (6) malignant disease. The author estimates that at least 100,000 cases are scattered over North China. Though it can occur in men, it is far more common

7. Swanson, W. W., and Iob, L. V.: Calcium and Phosphorus Content of Offspring After Feeding Vitamin D to Mother Rat, *Am. J. Dis. Child.* 49:43, (Jan.) 1935.

8. Liu, S. H.; Hannon, R. R.; Chu, H. I.; Chen, K. C.; Chou, S. K., and Wang, S. H.: *Chinese M. J.* 49:1, 1935.

9. Maxwell, J. P.: *Chinese M. J.* 49:47, 1935.

in women; pregnancy, which adds an extra drain on the calcium store, is largely the cause. Means of prevention may be divided into three parts: (1) general—sunshine and exercise; (2) dietary—health-giving, adequate diet; (3) medicinal—any one of the vitamin D preparations on the market.

#### CHRONIC ARTHRITIS

*Hyperpyrexia in Arthritis.*—Hench and his associates<sup>10</sup> report their results with the use of fever therapy in infectious and in gonorrheal arthritis. They found that infectious (atrophic) arthritis responds poorly to fever therapy. Of 60 patients so treated, none were completely relieved, 18 per cent were markedly relieved, 12 per cent moderately relieved, 20 per cent slightly benefited, and 50 per cent received no benefit. On the other hand, of 16 patients with gonorrheal arthritis, 90 per cent were either cured or markedly relieved. The authors feel that fever therapy provides direct sterilization of the affected joints, not only in the acute but also in the chronic stages of the disease.

Short and Bauer<sup>11</sup> of the Massachusetts General Hospital also treated a group of patients suffering from rheumatoid arthritis by diathermy, producing hyperpyrexia, with essentially similar results. Of 25 patients receiving 71 treatments, 20 per cent showed no improvement at any time, and 80 per cent showed temporary improvement, which was maintained in 20 per cent until the end of the follow-up period. The authors conclude that although the treatment injured none of the patients, it was such an ordeal that only in an occasional case is the use of diathermy justified in the treatment of rheumatoid arthritis.

Atsatt and Patterson<sup>12</sup> found that 7 of 8 patients with gonorrheal arthritis were completely relieved by artificial fever therapy.

EDITORIAL NOTE.—From these and other reports in the literature it seems that hyperpyrexia is not indicated in the usual cases of atrophic arthritis, but that in cases of gonorrheal arthritis it offers one of the most effective methods of treatment.

#### POLIOMYELITIS

*Active Immunization Against Poliomyelitis.*—Brodie,<sup>13</sup> after discussing the ineffectiveness of isolation and other measures for the con-

10. Hench, P. S.; Slocumb, C. H., and Popp, W. C.: Fever Therapy: Results for Gonorrheal Arthritis, Chronic Infectious (Atrophic) Arthritis and Other Forms of "Rheumatism," J. A. M. A. **104**:1779 (May 18) 1935.

11. Short, C. L., and Bauer, W.: Treatment of Rheumatoid Arthritis with Fever Induced by Diathermy: Follow-Up Study, J. A. M. A. **104**:2165 (June 15) 1935.

12. Atsatt, R. F., and Patterson, L. E.: California & West. Med. **42**:94, 1935.

13. Brodie, M.: Am. J. Pub. Health **25**:54, 1935.



trol of poliomyelitis, ventures the prophecy that effective and practical vaccination against this disease will soon be possible. He describes experiments on monkeys and on 12 children in which various inactivated virus suspensions were used. A virus suspension inactivated with solution of formaldehyde was most effective in producing antibodies in monkeys. The usual vaccine dosage was 5 cc. of the virus suspension in one or two doses. The duration of the immunity is not known, but in the monkeys used in the experiments it has lasted for two years.

*The Problem of Immunization Against Poliomyelitis.*—Schultz and Gebhardt<sup>14</sup> report from the bacteriologic laboratory of Stanford University their attempts at passive and active immunization of monkeys against poliomyelitis. Of 91 monkeys which received immune serums (about 5 cc. per kilogram) only 28 or 30 per cent escaped infection. Seven per cent of the 27 control animals also escaped infection. A relationship was noted between infection and the dose of virus given. For protection against a given dose of virus a disproportionately high concentration of antibodies was necessary. It was noted that the administration of immune serums tended to prolong the period of incubation but did not seem to lessen the degree of paralysis once infection was established. An attempt was made to immunize actively 15 monkeys with virus suspensions inactivated with 0.1 per cent formaldehyde. Twenty-four days after the final injection for immunization the animals were inoculated intracerebrally with the poliomyelitic virus, and all acquired poliomyelitis. In another series (number not given) the Kolmer technic was used to immunize the monkeys. All of these animals subsequently were inoculated, and in all of them poliomyelitis developed. The authors feel that artificial immunization is difficult since it seems to be developed on active neural infection. The immunity which develops on the administration of vaccines is humoral rather than cellular, and its durability as well as its degree is questionable.

#### THE BACK

*Mechanics of Physical Signs in Injuries of the Lower Parts of the Trunk.*—Brahdy<sup>15</sup> discusses the various mechanical difficulties occurring in injuries to the lower part of the trunk, i. e., sacro-iliac and lumbosacral strain, lesions of the hip joint, coccygodynia, gluteal bursitis, muscle spasm, etc. He gives a good review of the physiology of the normal motions of the trunk and explains the mechanics of the various injuries mentioned. He furnishes a good review of the entire subject.

14. Schultz, E. W., and Gebhardt, L. P.: *California & West. Med.* **43**:111, 1935.

15. Brahdy, L.: *Surg., Gynec. & Obst.* **60**:802, 1935.

## NEOPLASMS

*Endothelial Myeloma, or Ewing's Sarcoma.*—As a part of a symposium on the treatment of primary tumors of the bone, Coley<sup>16</sup> reports results from the treatment of Ewing's sarcoma by means of a mixture of cultures of *Streptococcus erysipelatis* and *Bacillus prodigiosus*, either alone or in combination with radiation. His conclusions are: 1. Irradiation as the primary method of treating operable endothelioma of the long bones should be abandoned except in the presence of a condition that renders amputation inadvisable. 2. While the brilliant results of conservative treatment (with toxins and radiation) in a number of cases of inoperable endothelial myeloma, some with extensive metastases, seem to justify an attempt to save the limb in early operable cases, the actual results of conservative treatment in such cases have been so poor that its continuation is not justified. 3. The results of surgical intervention alone cannot be determined from his own series, as he has not used the method in a single case. The Johns Hopkins Hospital group treated in this way shows 10.6 per cent well for five years. 4. While the group treated with toxins alone shows the highest percentage of five year cures, the majority of these patients were treated by other men under his direction and he has no way of knowing the number of failures not reported; hence he cannot give the exact percentage of five year cures with toxins alone. 5. The results obtained by early amputation followed by prolonged treatment with the aforementioned toxins seem to suggest this as the method of choice.

*Place of Biopsy in Bone Sarcoma.*—Every sentence of Ewing's<sup>17</sup> short article is of such significance that the article does not lend itself to abstracting. Only the motivating sentences of this very instructive paper can be given here. The paper itself is recommended for study. He states: 1. The biopsy should be the last step in the diagnosis of bone sarcoma. The clinical history and the roentgen observations, in experienced hands, yield a positive or a practically certain diagnosis in the majority of cases. 2. The whole clinical and roentgen picture usually furnishes a better conception of the diagnostic and therapeutic problem than can be obtained from a biopsy. 3. Few surgeons realize the limitations of the histologic diagnosis of bone tumors and the conditions which simulate or accompany them. (These are described in detail.) 4. Numerous unexpected complications arise from biopsies on bone tumors, and while the individual surgeon may claim that he has not encountered them very often, the total damage done forms a serious objection to the biopsy. 5. Bone sarcomas are allowed to run along,

16. Coley, W. B.: *Am. J. Surg.* **27**:7, 1935.

17. Ewing, J.: *Am. J. Surg.* **27**:26, 1935.

in the hands of all types of practitioners, until the disease becomes so obvious that no further delay can be tolerated and resort is finally made to the roentgenogram and then to biopsy. So long as this attitude prevails there will be few cures. 6. An aspiration biopsy by bore needle has been remarkably successful in revealing the structure of bone tumors. When this method becomes a familiar routine there will remain a very restricted field for the old surgical biopsy.

*Myeloma.*—According to Mathias,<sup>18</sup> the myeloma lies in the boundary region between bone tumors and hemoblastoses. It apparently arises from all the immature elements of the bone marrow. Its clinical varieties are many. The author reports the occurrence of a tumor of the skull in a 65 year old man. Radiation was used twice. Thereafter surgical excision was performed. A completely circumscribed tumor involving the dura mater was removed together with the overlying scalp. Histologic examination revealed a myeloma with the cell structure of a plasmocytoma. Elsewhere no evidence of neoplastic formation could be found. Eighteen months after operation the patient was still entirely well and clinically free from metastases. The author remarks that there may be, as in this case, isolated surgically accessible myelomas.

*Cancer Metastases in Bone.*—Fort<sup>19</sup> reviews the histories of 308 cases of cancer in which metastases were observed in bone. He found that carcinoma of the breast and of the prostate were responsible for from 50 to 70 per cent of the cancer metastatic in bone. Hypernephroma and carcinoma of the colon, thyroid, lungs and uterus metastasized frequently; metastases from cancer in other localities were rare. Metastases from cancer of the skin were very rare (2 cases of melanoma in the author's series). The most frequent sites of metastases were the pelvis, spine, ribs, femur and skull in the order named. Osteoclastic metastatic lesions were four times as frequent as osteoplastic.

#### ROENTGEN TECHNIC

*Roentgen Evidence of Injuries to the Attachment of the Supraspinatus Tendon.*—Henry<sup>20</sup> cites 6 cases to demonstrate that by an anterior-posterior view of the shoulder, with use of soft tissue roentgen technic and with the arm in adduction and extreme external rotation, the point of insertion of the supraspinatus tendon will be shown in silhouette on the humerus. His findings agree with those of Codman and others: 1. Immediately after injury fine spicules of bone appear. 2. Within a few weeks irregularity in the density of the evulsed surface

18. Mathias, E.: Beitr. z. klin. Chir. **161**:79, 1935.

19. Fort, W. A.: Radiology **24**:96, 1935.

20. Henry, L. S.: Am. J. Roentgenol. **33**:486, 1935.

and rounding of the tuberosity are seen. 3. From six months to a year later irregular calcification and occasional cysts with loss of prominence of the tuberosity and disappearance of the sulcus are evident.

*Roentgen Examination of the Lumbosacral Articulation.*—Williams and Wigby<sup>21</sup> find it helpful to take a lateral view of the lumbosacral region before the anteroposterior one in order to determine the anteroposterior tilt of the sacral angle, which varies in different persons. In order to have the central ray of the tube pass between the fifth lumbar and first sacral vertebrae in taking a lateral exposure a point is chosen 2 inches (5.08 cm.) below the iliac crest and 4 inches (10.16 cm.) behind the anterior and superior iliac spine. Also the following factors require consideration: (1) superimposition of the anterior superior iliac spines, (2) elevation of the dorsal spine to eliminate sagging of the lumbar vertebral column, and (3) extension of the hips to give the true standing relation of the articulating facets.

*Lateral Roentgenography of the Neck of the Femur.*—Jones<sup>22</sup> describes a technic for eliminating distortion by means of a curved cassette of special design which is shaped to be somewhat parallel to the curve formed by the shaft and neck of the femur. Haziness of outline has been largely removed by using a lead foil and silk filter together with a more favorable object-film distance ratio. Ability to show the head of the femur has been improved by twisting the trunk and shoulder of the patient out of the way of the x-ray tube.

#### MISCELLANEOUS

*Injuries to Vertebrae and Intervertebral Disks Following Lumbar Puncture.*—An interesting report of injuries to the spine from lumbar puncture is made by Pease.<sup>23</sup> The findings in 12 cases are given, which show a thinning of the intervertebral disks and a definite sclerosis of the vertebral bodies due to loss of nuclear substance and irritation of the bone. Pease experimented on cadavers and found several possible terminations of the needle when it is pushed beyond the neural canal: (1) the intervertebral disk, (2) a vertebra, (3) interarticular facets, and (4) venous sinusoids in the vertebral body. Brief anatomic considerations, a description of the mechanism of production and clinical considerations including detailed reports of 3 cases with roentgenograms comprise the paper.

*Cartilaginous Inclusions in Rachitic Bones.*—McMaster<sup>24</sup> studied at autopsy the long bones of a child which presented evidence of healed

21. Williams, P. C., and Wigby, P. E.: *Am. J. Roentgenol.* **33**:511, 1935.

22. Jones, L.: *Am. J. Roentgenol.* **33**:504, 1935.

23. Pease, C. N.: *Injuries to Vertebrae and Intervertebral Disks Following Lumbar Puncture*, *Am. J. Dis. Child.* **49**:849 (April) 1935.

24. McMaster, P. E.: *J. Bone & Joint Surg.* **17**:373, 1935.

rickets and discovered epiphyseal and metaphyseal cartilaginous inclusions. Inclusions of the same type were produced experimentally in rachitic rats. Because of the persistence of such cartilaginous rests the author suggests that they may act as a source for the development of cartilaginous tumors of bone.

*Treatment of Primary Myopathies.*—A discussion based on a review of the theories concerning the production of creatine as well as its relation to the amino-acids is offered by Reese and his co-workers.<sup>25</sup> They stress the theory that creatine depletion secondary to nonutilized glycine in the dystrophic muscles is responsible for the disturbed physiologic process. Glycine therapy is discussed, and cases are reported. It is concluded that therapy by means of endocrine and pharmacologic stimulation has proved unsatisfactory. Therapy by glycine or glutamic acid, on the other hand, is encouraging and recommended as the best available. Clinical and biochemical investigation seems to indicate that the amino-acid therapy is effectual; cures are not obtained, but rather definite clinical remissions.

*Anomalies of Two Muscles in the Living.*—Two muscular anomalies observed in the living are reported by Sauser,<sup>26</sup> and the difficulties which such anomalies might present in diagnosis are discussed. The first of these anomalies was a sternal muscle which was present only on one side and presented a tumor-like swelling lateral to the lower portion of the sternum. The second anomaly was an extensor of the hand from the midportion of the distal row of carpal bones to the base of the third metacarpal bone. On contraction it appeared as a soft tumor-like mass on the dorsum of the hand. A review of the literature of these rare anomalies is given.

#### CIRCULATORY DISTURBANCES OF THE EXTREMITIES

*Results of Lumbar Sympathectomy in Spontaneous Gangrene.*—Filatov<sup>27</sup> discusses his experience with sympathectomy in what is termed in this country "thrombo-angiitis obliterans." The immediate result in 34 patients was as follows: In 1 it was brilliant; in 16, good; in 11, satisfactory; in 5 there was no effect; 1 death occurred, following a wound infection. The end-results in 14 patients examined a year or more after operation were as follows: 9 remained well. In 2 patients seen within from one to two years after operation, some pain and tiring recurred, but no necrosis or gangrene. All of these patients maintained their hyperthermia of from 1 to 2 C. In the remaining 3 patients, the disease recurred six months, two years and three years

25. Reese, H. H.; Burns, E. M., and Rice, C. M.: Treatment for Primary Myopathies, Arch. Neurol. & Psychiat. 33:19 (Jan.) 1935.

26. Sauser, G.: Wien. klin. Wchnschr. 48:430, 1935.

27. Filatov, A.: Deutsche Ztschr. f. Chir. 244:491, 1935.

after operation but there was no gangrene (a fact the author attributes to the operation). The author emphasizes that the indications of Adson and Brown (demonstration that the vessels are still capable of dilatation, as measured by comparison of the temperatures of the extremity and the body) should be followed.

#### ORTHOPEDIC OPERATIONS

*Arthrodesis for Tuberculosis of the Hip.*—Harris<sup>28</sup> uses a combined intra-articular and extra-articular method of hip fusion for tuberculosis, using a large rectangular flap of ilium and securing it with bone screws to the superior rim of the acetabulum and to the denuded neck of the femur. Of 22 operations performed by this method, 16 obtained bony union; in 4 additional cases the condition was greatly improved; 1 patient died of postoperative pulmonary embolism; in another the hip was still in plaster fixation.

*Closure of Cavities from Chronic Osteomyelitis by Plastic Methods.*—In cases of long-standing osteomyelitis of long bones, Lord<sup>29</sup> advocated the removal of the diseased bone and the introduction of fat, fascia and muscle tissue into the cavity, with primary loose closure of the skin flap. A Dakin tube is usually brought out at each end of the wound. He states that in some cases complete closure and healing of the wound have been accomplished in two weeks. Illustrative cases are described, and the operative technic outlined.

*Treatment of Pseudo-Arthrosis of the Long Bones with a Rib Transplant.*—Brewer<sup>30</sup> advocates the use of rib grafts instead of the tibial grafts in the repair of pseudo-arthroses. He removes one, two or even three ribs in the region between the anterior axillary and mammary lines. The ribs are removed together with the periosteum. He overlaps the site of the fracture for 2 cm. and holds the ribs against the site of fracture with the aid of a metallic wire above and below. The ribs are split lengthwise on one side and opened up, like a book, before being applied to their bed. Three cases are reported with satisfactory union.

EDITORIAL NOTE.—This procedure has been utilized for the clavicle with some success. However, tibial or iliac grafts for routine use seem easier to obtain and shape and seem to be more adequate in size, and with them metallic fixation is not required.

*Therapy of Epicondylitis Humeri (Tennis Elbow).*—Since the muscles arising from the external epicondyle are involved in the symp-

28. Harris, R. I.: J. Bone & Joint Surg. **17**:318, 1935.

29. Lord, J. P.: Surg., Gynec. & Obst. **60**:853, 1935.

30. Brewer, F.: Deutsche Ztschr. f. Chir. **244**:445, 1935.

period of disability was eight and one-third months, and the longest was fourteen months. Five patients failed to return to preinjury activity.

EDITORIAL NOTE.—This article describes fully the pathologic changes in vertebral fractures and the resultant injury to the intervertebral disks and vertebral bodies. The details of reduction by hyperextension are carefully outlined, and the end-results obtained from this type of treatment are shown to be excellent. The article should be read in its entirety by all who are treating such fractures.

*Fractures and Dislocations of the Cervical Spine.*—From a study of 45 fractures or dislocations of the cervical spine, Hudson<sup>37</sup> concludes that conservative measures, i. e., traction on the head followed by immobilization in the plaster of paris cast, gave the best results. No laminectomies or spinal fusions were performed in this series. Fractures of the fifth and sixth cervical vertebrae were the most common, and the transverse processes, odontoid process, spinous processes, laminae and pedicles were injured in that order of frequency. There were 4 unilateral dislocations of the atlas on the axis. These were reduced by manipulation under general anesthesia. The author thinks that the patients with immediate signs of complete paralysis have a hopeless outlook for recovery. Those with no evidence of injury of the cord have an excellent chance for recovery, whereas those with incomplete or delayed injury of the cord have a fair chance for recovery. In his series of 45 cases there were 6 deaths.

*Pathologic Study of Fracture of the Femoral Neck After Treatment with the Smith-Petersen Nail.*—Nystrom<sup>38</sup> of Uppsala reports the results of 29 operations by use of the Smith-Petersen nail for fractures of the femoral neck. Three patients died a short time post-operatively. In 24 patients good reduction was obtained. In 6 patients a separation of the fragments was observed during convalescence which would probably go on to nonunion. In several cases the nail bent or broke, probably from too early weight bearing. The author feels that the method is of help in permitting patients to move about more freely in bed, but that weight bearing should be delayed for at least two months.

*Fractures of the Femoral Neck Treated by Blind Nailing.*—O'Meara<sup>39</sup> reports 12 cases of fracture of the femoral neck, 11 transcervical and 1 at the base treated by "blind nailing" with a flanged nail. Under anesthesia the fracture was reduced by manipulation. Antero-posterior and lateral roentgenograms were then taken. If satisfactory

37. Hudson, O. W.: J. Bone & Joint Surg. **17**:324, 1935.

38. Nystrom, G.: Acta chir. Scandinav. **76**:1, 1935.

39. O'Meara, J. W.: New England J. Med. **212**:43, 1935.

reduction had been obtained, a 3 to 4 inch (7.6 to 10 cm.) incision was made on the lateral side of the thigh distal to the greater trochanter and a Smith-Petersen nail was driven from below the trochanter into the femoral neck. The angle of insertion and the length of the nail were determined with a protractor on the anteroposterior roentgenograms. After the nail had been driven half-way into the femoral neck roentgenograms were taken again; and if the direction and position of the nail were satisfactory, the nail was driven full length into the bone. The leg was kept in a Thomas splint with 5 pounds (2.3 Kg.) of traction for from three to four weeks. Weight bearing on the leg was permitted after two months. No walking caliper was used. The nail was removed in each case after six months. The study of the end-results showed that 9 patients were bearing weight. Seven in whom the nail had been removed had bony union. One patient died of carcinoma. Two were treated too recently for a study of end-results to be made.

*Crushing of One Tuberosity of the Tibia.*—Sechehayé<sup>40</sup> reports 14 cases of unilateral crushing of the upper end of the tibia in which the injury was treated by operative means and 6 cases in which it was treated by closed methods. Roentgenologic tracings are given in all cases. The operative treatment was much more successful and consisted in levering up the depressed condyle, after opening the joint so as to restore, under direct vision, the contour of the articular cartilage, and supporting the replaced fragments with a bone graft driven horizontally and acting as a supporting shelf. If the semilunar cartilage was damaged, as it frequently was, it was removed.

*Treatment of High Tibial Fractures Extending into the Knee Joint.*—Kummer<sup>41</sup> advises, in cases of true oblique fracture of one or the other condyle of the tibia with malalignment of the joint, that the fractured portion be elevated into position and transfixed with an autogenous bone graft obtained from the same tibia. He reports 3 such cases, in which he used the graft rather than metal appliances. His cases had approximately one year's follow-up. He attempts a comparison of his group of fractures with a group of 15 treated conservatively. Of the latter, 11 showed arthritis deformans (duration after fracture not stated). He believes the operative procedure to be of value in averting such changes.

*Epiphyseal Fracture and Dislocation at the Elbow Joint.*—Howard<sup>42</sup> found that separation of the lower humeral epiphysis with dislocation of the epiphysis (capitellum and trochlea or capitellum alone)

40. Sechehayé, L.: J. de chir. 45:561, 1935.

41. Kummer, A.: Zentralbl. f. Chir. 62:503, 1935.

42. Howard, N. J.: J. Bone & Joint Surg. 17:123, 1935.



occurred in 7.2 per cent of injuries to the elbow. There is danger of overlooking the element of dislocation and treating the injury simply as an epiphyseal separation. Closed reduction is difficult, and operation is often necessary. Reduction when incomplete is followed by extreme loss of function.

*End-Results of Fractures of the Distal Radial Epiphysis.*—Aitken<sup>43</sup> studied the clinical and roentgenologic end-results in 60 cases of injury to the lower radial epiphysis at periods ranging from two to nine years after injury. He found surprisingly little deformity and very slight interference with growth resulting from such injury. In 34 cases the reduction of the displaced epiphysis was not accurate, yet in none of the cases was there any deformity even if the final displacement amounted to one quarter or one half of the thickness of the shaft. Repeated manipulations seemed to have no bad effect on the end-result. Because malposition was a rare end-result, he feels that osteotomy is never justified.

*Fractures of the Forearm.*—Hein<sup>44</sup> presents a complete review of 415 fractures of the forearm of all types including fractures of the upper and lower ends as well as of the shaft. Good results were obtained in 87 per cent of the cases. Nonunion occurred in only 7 per cent of the cases. Union was less rapid in patients operated on than in those treated by closed reduction.

EDITORIAL NOTE.—The article gives a comprehensive review of the subject of forearm fractures and is well worth reading.

*Fractures of the Wrist in Childhood, Puberty and Adolescence.*—Gillies<sup>45</sup> concludes that before closure of the epiphyseal line age bears an important relationship to the type of fracture that occurs. In childhood the characteristic fractures are either transverse or "torus" (the so-called garden hose type). At puberty the typical injury is separation of the epiphysis with posterior displacement.

*Healing of Phalangeal Fractures.*—In 100 consecutive cases Smith and Rider<sup>46</sup> found that the average time for bony healing of complete phalangeal fractures, as determined roentgenologically, was five months. Clinical healing took about one quarter of this time or about five weeks and was considered as embracing the period that elapsed from the time of the injury to that of the return to the former occupation. Fracture lines were usually more distinct at the end of thirty days than at the time of injury. Lack of bony union could not be assumed until at

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43. Aitken, A. P.: J. Bone & Joint Surg. **17**:302, 1935.

44. Hein, B. J.: J. Bone & Joint Surg. **17**:272, 1935.

45. Gillies, C. L.: Iowa State J. Med. **25**:15, 1935.

46. Smith, F. L., and Rider, D. L.: J. Bone & Joint Surg. **17**:91, 1935.

least a year's time had elapsed. Splints were kept on about two weeks except in cases of "baseball finger," in which the injured member was splinted longer.

# RESEARCH

*Stimulation of Healing in Nonhealing Wounds by Allantoin.*—Robinson<sup>47</sup> ascertained that allantoin is an important excretory product of the maggot. He believes that it is responsible for at least some of the beneficial effect of maggots on septic wounds. It is not claimed that allantoin may entirely replace the maggot, because the maggot, in addition to secreting allantoin, has the ability to carry off detritus. Allantoin, however, is bland, stable and harmless, can be obtained at rather low cost and stimulates healing of wounds.

*Experimental and Clinical Study of Traumatic and Hemorrhagic Shock.*—Coonse and his co-workers<sup>48</sup> show by numerous charts from observations and studies on experimental animals that traumatic differs from hemorrhagic shock in that the former is characterized by increasing acidosis and a relative increase of blood cells over blood serum, the latter by a lack of acidosis and a relative increase of serum over blood cells. In slow hemorrhage, however, the findings more clearly resemble those of traumatic shock and usually show depression of the higher centers, increasing anoxemia of tissue and acidosis. Laked blood and traumatized muscle seem to be factors which produce the toxic and depressant effect on the vital centers. Hemolysis is constantly found in traumatic shock. Acute hemorrhagic shock is best treated by replacement of the lost volume of blood with whole blood or with intravenous saline, dextrose or acacia solution. Traumatic shock, on the other hand, responds favorably to intravenous 5 per cent sodium bicarbonate solution, usually about 40 cc. This can be repeated every half hour or at longer intervals. Such treatment seems to prevent acidosis, serves as a stimulant to the vital centers, increases the rate of dissociation of oxyhemoglobin and improves the peripheral blood flow. In certain cases supplementary inhalations of carbon dioxide and oxygen may be helpful for mechanical effects. Summaries of the records on observations in 7 clinical cases are appended which show the results of the alkaline therapy.

*Repair of Articular Cartilage in Young Dogs.*—Bennett and Bauer<sup>49</sup> compared the reparative changes in surgical defects of the central non-weight-bearing articular cartilage of the knee joint of the puppy with the changes in similar lesions in the adult dog previously reported.<sup>50</sup>

47. Robinson, W.: J. Bone & Joint Surg. 17:267, 1935.

48. Coonse, G. K.; Foisie, P. S.; Robertson, H. F., and Aufranc, O. E.: New England J. Med. 212:647, 1935.

49. Bennett, G. A., and Bauer, W.: J. Bone & Joint Surg. 17:141, 1935.

50. Bauer, W., and Bennett, G. A.: Am. J. Path. 8:499, 1932.

These studies indicated that repair is no more rapid or complete in young puppies before closure of the epiphysis than it is in adult dogs. The proliferative activity of cartilage cells is greater in the deeper zones of the articular cartilage than in the more superficial zones. More active proliferation of cartilage cells was noted in lesions in which crevices existed.

*Increase of Neuromuscular Function in Partial Nerve Paralysis.*—Dogliotti<sup>51</sup> has found that if a nerve is sectioned the regenerating fibers multiply themselves considerably. On this assumption he believes that if a nerve is partially paralyzed (as after poliomyelitis) it can be sectioned and immediately sutured together again and the few vital nerve fibers will regenerate and multiply themselves, sending down the distal portion of the nerve many functioning fibers where before there were only a few. In dogs two thirds of the sciatic nerve was sectioned, dissected upward and side-tracked into muscle tissue. The remaining third of the nerve above was attached to the whole trunk below. Section was done at this point and the third of the trunk resectioned to the whole nerve below immediately. Complete paralysis of the limb naturally followed, but after from six to seven months there was normal use of the whole limb in spite of the fact that two thirds of the nerve was not functioning. Microscopic section showed that the upper nerve fibers had regenerated in such number that numerous branches had grown down and filled the whole trunk of the nerve. Section and suture were then done in a patient who had complete poliomyelitic paralysis of one leg except for slight flexion of the third, fourth and fifth toes, a trace of plantar flexion and a possible trace of contraction of the triceps (gastrocnemius?). This patient had been paralyzed for eight years. Fifteen months after operation the patient had a return of the power of flexion of all the toes. Four years later there was, in addition, power in the posterior muscles of the calf and thigh. There were flexion of the knee, extension of the ankle and flexion of all the toes.

EDITORIAL NOTE.—Function of the knee, ankle and toes is described as *balide*, or healthy. How strong a function this represents we do not know.

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51. Dogliotti, A. M.: J. de chir. 45:30, 1935.

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## PALLIATIVE IRRADIATION OF GASTRIC CANCER

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Radium and roentgen therapy have proved their worth in the treatment of cancer of the oral cavity, uterus, urinary bladder, skin, rectum and breast and of the various tumors of the lymphoid system. The stomach is the most frequent site of cancer, but unhappily it has not benefited by the advent of these new physical agents. Heretofore, radiation therapy has not been extensively employed in the treatment of gastric cancer because of the supposed radioresistance of this tumor and because of certain apparently insurmountable technical difficulties. We have been engaged for the past four years in the radiation therapy of cancers of the stomach chiefly in an attempt to afford palliation to the great number of patients with advanced inoperable cancers of this organ. This article is a recital of our experiences and conclusions concerning these experiments.

### HISTORICAL REVIEW

Shortly after Roentgen announced his discovery of the x-rays, an article appeared describing the use of this new agent in the treatment of cancer. It is of considerable interest to note that the first cancer so treated was situated in the stomach. It was Despeignes<sup>1</sup> who in 1896 published this report of a gastric cancer treated by eighty exposures to the roentgen rays, each of from fifteen to thirty minutes' duration twice a day. The patient's condition was improved, and he was relieved from pain.

Not until almost two decades later were there reports of other cases of gastric cancer in which irradiation was used. Wickham and Degrais<sup>2</sup> in 1914 cited one case of pyloric cancer in which a preliminary gastroenterostomy was performed, an opening distal in the stomach being left through which radium could be inserted. The applications were con-

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From the Memorial Hospital for Cancer and Allied Diseases.

1. Despeignes, V.: Observations on a Case of Cancer of the Stomach Treated by Roentgen Rays, *Lyon méd.* 82:428 (July) 1896.

2. Wickham, L., and Degrais, P.: Radium and Cancer, New York, Paul B. Hoeber, Inc., 1914.

tinued for three months, a catheter containing radium being inserted into the stomach and directed toward the pylorus, while at the same time the palpable tumor received external irradiation through the abdominal wall. The patient was vastly improved in health for eighteen months following this therapy.

Janeway<sup>3</sup> in 1918 treated seven patients with cancer of the stomach. He applied radium externally in most cases, but in one instance the stomach was opened and the radium was inserted into the cavity. He considered the improvement, as indicated by the reduction in the size of the tumor as well as by subjective relief, to be sufficient justification for employing this method in the palliative treatment of gastric adenocarcinoma, which is usually discovered after it has reached an inoperable stage.

Levin<sup>4</sup> in 1922 advocated the insertion of bare glass capillary tubes of radon into gastro-intestinal and retroperitoneal cancers. He cited cases of duodenal and intestinal carcinoma in which improvement was due primarily to this treatment, which was given twice through two different laparotomy wounds. He disapproved of the use of roentgen irradiation in this connection because of the severe cachexia it was said to induce, and, furthermore, he stated that radium used externally was ineffectual.

Evans and Leucutia<sup>5</sup> (1923) reported twenty-five cases of carcinoma of the stomach in which high voltage roentgen rays were used. The improvement noted led them optimistically to declare that in combination with surgical measures irradiation might possibly eradicate all early gastric cancers. Two such cancers disappeared after treatment, as determined by roentgenographic study, but recurred eight and twelve months later. Some patients with ascites experienced considerable relief from this condition after irradiation through the abdominal wall. All patients had more or less subjective relief from pain, vomiting and hemorrhages for a number of months. The authors urged in describing their technic that the lungs and the adrenal glands be avoided by projecting films of the kidneys and stomach on the body to aid in marking the fields and tilting the tube correctly. Holfelder and Peiper<sup>6</sup>

3. (a) Janeway, H. H.: *Gastrosocopy*, J. A. M. A. **61**:1339 (Oct. 11) 1913; (b) *The Action of Radium in Cancer*, Surg., Gynec. & Obst. **26**:233, 1918. (c) Janeway, H. H., and Green, N. W.: *Esophagoscopy and Gastrosocopy*, Surg., Gynec. & Obst. **13**:245, 1911. (d) Janeway, cited in Ewing, J.: *Early Experiences in Radiation Therapy*, Am. J. Roentgenol. **31**:153 (Feb.) 1934.

4. Levin, I.: *Intraperitoneal Insertion of Buried Capillary Glass Tubes of Radium Emanation*, J. A. M. A. **79**:2074 (Dec. 16) 1922.

5. Evans, W. A., and Leucutia, T.: *Results of Deep Roentgen Treatment of Gastro-Intestinal Malignancies*, Am. J. Roentgenol. **10**:793, 1923.

6. Holfelder, H., and Peiper, H.: *Die Strahlenempfindlichkeit der Nebennieren und Wege zur Verhütung von Nebennierenschädigungen in der Röntgentiefentherapie*, Strahlentherapie **15**:1, 1923.

published a report of experimental work on this subject in the same year, illustrating how a gastric tumor could be irradiated through three portals in such a way that one adrenal gland was always protected. It was stated that 60 per cent of a skin erythema dose to both adrenals is fatal. The dosage to the skin given by Evans and Leucutia<sup>5</sup> was from 110 to 130 per cent of a skin erythema dose through several portals cross-firing at the tumor. The factors of treatment were: 200 kilovolts; filter, 1.3 mm. copper and 1 mm. aluminum; port, 20 by 20 cm., and distance, from 40 to 60 cm. In their experience 140 per cent skin erythema dose is the maximum dose which does not damage the intestinal mucosa. They advocated a fat and acid-free diet and an abundance of alkalis for the patient together with cerium oxalate and essence of pepsin for radiation sickness.

In 1923 Neuman and Coryn<sup>7</sup> published a report of a case of carcinoma of the stomach with recurrence of the growth eleven months after subtotal gastrectomy in which radium needles were buried for six days, giving a dose of 3,456 milligram hours. The patient was comfortable, able to work and without symptoms for nine months. At that time external irradiation proved ineffective; the authors suggested that if the stomach had been fixed to the anterior abdominal wall at the time of the operation external irradiation might have been more successful.

Werner<sup>8</sup> (1925) described in detail such an operation for fixing an inoperable gastric tumor to the anterior abdominal wall so as to make it accessible for irradiation. It was originally suggested by Karl Beck and had been carried out by Werner and Caan and also by Wilms and Finsterer. The requirements for such a procedure are that the tumor must be movable and not too deeply seated. The irradiation is started a few days later, light doses (from one-half to three-fourths unit skin dose divided) being given, as a rapid breaking down of the tumor must be avoided. The anterior wall, made up of skin and peritoneum only, forms a scar which will contract, Werner said, and never develop a hernia. A repetition of the small doses is advised after from four to six weeks, although greater doses are indicated for the relief from pain in very advanced cases. Radium applied externally was said by this author to be ineffective.

Cahen<sup>9</sup> in 1923 also reported the treatment of two gastric cancers with radium used externally in moulages; both patients were in good health about ten months after the procedure.

7. Neuman, F., and Coryn, G.: *Récidive de cancer de l'estomac traité par l'aiguillage radifère*, *Cancer* 1:87, 1923.

8. Werner, R.: *Tumoren des Magen-Darm-Traktes*, in Gauss, C. J.: *Lehrbuch der Strahlentherapie*, Berlin, Urban & Schwarzenberg, 1927, vol. 2, p. 228.

9. Cahen: *Cancer de l'estomac*, *Cancer* 2:42, 1925.

Schmidt<sup>10</sup> in 1928 reported the results of irradiation of twenty-nine inoperable and one recurrent gastric cancer. Of twenty-two patients followed, one was living and well three years later, the diagnosis having been proved by histologic section of tissue removed during an exploratory laparotomy. Holfelder<sup>11</sup> published the reports of two cases; in one the patient lived two and one-half years and in the other the patient died more than a year after roentgen therapy; in the latter case there was no evidence of tumor, although the clinical and roentgenographic findings had been indisputable.

Possibly this lack of enthusiasm and abortive attempts to use irradiation for gastric cancer were influenced by the authors of several books and papers which appeared at about that time. Ewing,<sup>12</sup> in an analysis of radiation therapy in 1924, classified gastric cancer among the tumors that were not then amenable to irradiation, although he stated that he had seen in section a carcinoma of the pylorus which had been destroyed by irradiation. He also remarked that some palliative results had appeared remarkable. Laborde<sup>13</sup> (1925) wrote that cancer of the digestive tract other than that of the esophagus and rectum does not seem to be aided sufficiently by radiation therapy to warrant mention. Waring<sup>14</sup> (1928) mentioned radiologic methods in his book and stated that his experience was limited to the external application of radium for inoperable gastric cancer. F. C. Wood<sup>15</sup> classified the cells of cancer of the gastro-intestinal tract with melanoma as having a specific resistance to irradiation. Persons with gastric cancer are not even accepted for radiation therapy at Radiumhemmet in Stockholm.

Holfelder,<sup>16</sup> however, continued to write about and hope for results in the treatment of cancer of the stomach, and in 1931 he advocated the use of a compression diaphragm to exclude the organs overlying the tumor by pressure and the replacement with air, as much as possible, of the distance between the target and the tumor. He said that over a hundred gastric cancers had been so treated and recalled two

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10. Schmidt, W.: Die Ergebnisse der Röntgentherapie bösartiger Geschwülste an der chirurgischen Universitätsklinik zu Göttingen in den Jahren 1919-1927, *Strahlentherapie* **30**:201, 1928.

11. Holfelder, H.: Was kann man heute von der Röntgentherapie der sogenannten inoperablen Tumoren erwarten? *Strahlentherapie* **33**:131, 1929.

12. Ewing, J.: *An Analysis of Radiation Therapy in Cancer*, Radium Report of Memorial Hospital, second ser., 1923, New York, Paul B. Hoeber, Inc., 1924.

13. Laborde, S.: *La curiethérapie des cancers*, Paris, Masson & Cie, 1925.

14. Waring, H. J.: *Surgical Treatment of Malignant Diseases*, New York, Oxford University Press, 1928.

15. Wood, F. C.: Cell Resistance Incited by Radiation, *Am. J. Cancer* **16**: 1247 (Sept.) 1932.

16. Holfelder, H.: Methodische Fortschritte der Röntgentherapie der Kresbse des Verdauungskanaals, *Strahlentherapie* **42**:497, 1931.

patients who lived one year and two and one-half years, respectively, after treatment. The diagnosis in these cases had been verified before treatment by exploratory laparotomy and by biopsy. Von Haberer<sup>17</sup> (1931) and Boas<sup>18</sup> (1931) both mentioned the postoperative use of radiotherapy for prophylaxis and for recurrent and inoperable cancers. Yeomans<sup>19</sup> in 1933 cited the instance of a patient who lived two years and ten months after treatment consisting of gastro-enterostomy and interstitial irradiation by gold radon seeds.

Gosset, Monod and Regaud<sup>20</sup> recently reported their results in the treatment of thirty-one patients with gastric cancer at the Radium Institute of Paris. With all conditions equal, these authors expressed the opinion that the gamma rays of radium are more elective therapeutically than the roentgen rays—an observation verified in our present thesis. The treatment was limited to the external application of radium, a radiating surface of 150 sq. cm., a skin distance of only 10 cm. and multiple skin ports being used. At the beginning of their clinical experiment the authors raised the question whether or not the cure of gastric adenocarcinoma by irradiation would necessitate the administration of a dose of radiation incompatible with the integrity of the normal mucosa of the digestive tube. Thirty-one gastric cancers, thirty of which were diagnostically verified by exploratory laparotomy, were treated by this method. Seventeen of the patients had no amelioration of symptoms and no prolongation of life. In seven definite improvement was observed; but the duration of survival was not increased. In the remaining seven an important and considerable betterment in health was accompanied by a notable prolongation of life. The results in this group were as follows: One patient was cured for six and one-half years, another patient was living after thirty-three months and five patients died after eleven, twelve, sixteen and twenty-one months and four years and nine months. Two factors exerted an unfavorable influence on these results: the poor general state of the patient and the radioresistance of the cancers. The radiosensitivity of gastric cancer is held to be extremely variable, as judged by the great discordance in comparing the doses with the results of irradiation. Gosset, Monod and Regaud considered the most fertile field for their scientific experiment to be the local recurrences after gastrectomy, as here they were

17. von Haberer, H.: Magen und duodenal Krebs, *Neue deutsche Klin.* **7**: 90, 1931.

18. Boas, I.: Der Magenkrebs, *Neue deutsche Klin.* **7**:59, 1931.

19. Yeomans, F. C.: Care of Advanced Carcinoma of the Gastro-Intestinal Tract, *J. A. M. A.* **101**:1141 (Oct. 7) 1933.

20. Gosset, A.; Monod, O., and Regaud, C.: Traitement des cancers gastriques inextirpables par le radium à distance, *Bull. Acad. de méd., Paris* **110**:379 (Nov. 21) 1933.



supplied with the original tumor for histologic analysis and evaluation of radiosensitivity. They agreed that gastrectomy or pylorotomy is preferable to radiation therapy whenever the cancer is operable.

#### EXPERIMENTS IN IRRADIATION OF THE NORMAL STOMACH

The histologic and functional changes induced by irradiation of the normal stomachs of animals and human beings have been thoroughly studied. Regaud, Nogier and Lacassagne<sup>21</sup> in 1912 irradiated the abdomens of dogs with roentgen rays with the production of acute or chronic gastric ulcers, depending on the dosage and the time of survival of the animal. Ghilarducci<sup>22</sup> (1914 and 1916) observed that roentgen irradiation of rabbits caused the chief cells to disappear earlier than the parietal cells; this differential sensitivity was later confirmed by Regaud and Lacassagne.<sup>23</sup> Radium placed within the cavity of the stomach also destroyed the chief cells first; these cells were replaced by the hypertrophic parietal cells, which subsequently disappeared. The mucous cells finally lost their function and slowly degenerated. Tsukamoto irradiated the livers of rabbits and produced hemorrhages and ulcers in the gastric mucosa. No definite alterations were found in the stomachs of dogs after exposure of other parts of their bodies to the roentgen rays.

The functional disturbances in the stomachs of dogs following roentgen irradiation were fairly constant; single small doses evoked no change; larger doses caused the acidity to fall sharply each time, to remain low for several days and then to rise gradually, returning to normal after the irradiation was discontinued. The pepsin content fell slowly after repeated exposures and rose sluggishly back to normal during the postirradiation period. Roentgen irradiation of the stomachs of patients with simple hyperchlorhydria and hyperacidity associated with chronic ulcer caused in the majority of cases a reduction in the gastric acidity, both free and total. This change was more rapid for simple hyperchlorhydria, but in all instances it was transient after a single exposure, returning to normal in twenty-four hours. With each subsequent roentgen treatment the acidity was still more reduced and the effect was more lasting. The greatest diminution followed when the initial acidity was highest. Radiotherapy for gastric ulcer has been

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21. Regaud, C.; Nogier, T., and Lacassagne, A.: *Action mœve des rayons X sur le tube digestif*, Paris méd. 8:489, 1911-1912.

22. Ghilarducci, cited by Desjardins, A. U.: *Action of Roentgen Rays and Radium on the Gastro-Intestinal Tract*, Am. J. Roentgenol. 26:145 (July); 335 (Aug.); 493 (Sept.) 1931.

23. Regaud, C., and Lacassagne, A.: *Effets des radiations sur les muqueuses du tube digestif, sur les épithéliums de revêtement et sur les glandes exocrines et endocrines*, Radiophys. et radiothérapie 1:70, 1930.

attempted independently by Matoni and Strauss, who reported considerable initial improvement. Winternitz (1911) added radium emanation to water or test meals given to normal subjects and to patients with hypo-acidity and hyperacidity. He found no changes in the acid or pepsin content of the succus gastricus or in the gastric motility.

#### DISADVANTAGES AND DANGERS IN IRRADIATION OF GASTRIC CANCER

We may enumerate briefly the apparent disadvantages attendant on radiation therapy of gastric cancer. First, the stomach is an essential organ needed daily for the ingestion of food. It is at the gateway of the alimentary canal, and the preservation of its function together with the appetite and the ability to utilize a minimal amount of food is absolutely necessary for the integrity of the patient. If it were possible for the stomach to have complete rest for six weeks during the progress of the treatment, the results would be much more satisfactory. The inaccessibility of the stomach is another disadvantage if one compares it with the uterus, skin, mouth, rectum and breast, which are readily accessible to roentgen irradiation and to the implantation of radium. The stomach is so deep within the body cavity that in all attempts to treat a tumor of this organ with roentgen rays or radium delivered from external sources only a small percentage of the dose on the skin reaches the tumor substance. It is a mobile organ and is not constantly in the same relation to the anterior and posterior abdominal walls, to which the irradiation must be given. The difficulty of delivering a depth dose of any magnitude is of great importance when one realizes that the majority of carcinomas of the stomach are radioresistant tumors.

To increase the tissue dosage of radiation in cases of cancer of the stomach would require the implantation of radium by a laparotomy. Hence one may appreciate that the surgical approach for interstitial irradiation of carcinoma of the stomach is a more dangerous procedure than for radium therapy of any other tumor, with the exception of a neoplasm of the brain. It is far more serious than the surgical exposure of metastatic carcinoma in cervical, axillary or inguinal lymph nodes, than suprapubic cystotomy for the implantation of radium in the bladder or than laryngotomy for the treatment of laryngeal carcinoma. The mortality rate from the operation alone is not insignificant. Direct examination of the interior of the stomach by means of the gastroscope, while possible and useful at times in obtaining specimens for biopsy, does not offer a practical means of inserting radium into the gastric cancer.

One of the major obstacles in radiation therapy is the same that confronts the surgeon, namely, the advanced stage of the tumor when the diagnosis is made, i. e., the state of inoperability. This militates

against successful treatment by radium and roentgen rays just as it removes the possibility of complete surgical extirpation. As long as the carcinoma is confined to the stomach there may be means of overcoming the technical difficulties of implanting sufficient radium or delivering a depth dose of radiation from external sources sufficient to control the carcinoma, but when metastasis has occurred to the liver or the peritoneum the patient is beyond all hope even of palliation from irradiation. This is due to the fact that the liver parenchyma is as sensitive as the carcinoma to the effect of irradiation: There does not exist that selective radiosensitivity on which successful radiation therapy depends.

One of the essential requisites for good results in the irradiation of carcinomas of other organs is that the patient be in good general health. In cases of gastric cancer this is seldom the case; most of the patients are emaciated, cachectic, anemic, undernourished and unable to face the rigor and ill effects of a long program of radiation therapy.

The close proximity of such organs as the liver, pancreas and adrenal glands to the majority of gastric cancers handicaps the radiologist in the use of external irradiation. Only by careful localization of the gastric tumor and selection of the region for irradiation is it possible to administer this treatment without consequent injurious effects on these adjacent labile organs. The so-called radiation sickness is a common accompaniment of external irradiation of almost all parts of the body, but it is particularly frequent and severe following roentgen irradiation of the upper portion of the abdomen. Radiologists have avoided direct irradiation in cases of mammary cancer by directing the beams tangential to the chest, but such a procedure is not possible in the deep tumors, such as those of the stomach. The severity of the radiation sickness following the treatment of gastric cancer may greatly delay convalescence; furthermore, it may be so distressing during the treatment that it limits the amount of radiation which may be applied besides increasing the time during which the treatment is given, this being a most important factor.

Many carcinomas of the stomach are situated at one of the gastric outlets, the cardia or the pylorus. These cancers are first made manifest frequently by symptoms of obstruction. A patient with partial or almost total obstruction either at the cardia or at the pylorus is certainly not a fit subject for irradiation. In such a case surgical intervention is indicated and radiation therapy reserved as a postoperative measure. We have been able to bring about improvement in cases of partial obstruction of the pylorus or the cardia, but if the obstruction is nearly complete the urgency is too acute to wait for the late effects of radiation therapy as it requires from three to six weeks for the results to become evident.

Practically all gastric cancers are infected, and infection diminishes the radiosensitivity of any cancer. During the first few days of irradiation fever may develop, suggesting that the infection has increased. but later the fever vanishes and the evidences of infection also disappear.

The stomach being a hollow viscus, the dangers caused by the implantation of radium in its wall are considerable. Great accuracy in the implantation of radium is necessary, since all precautions must be taken to prevent leakage of the gastric contents at the time of treatment as well as later due to overdosage. The dangers of radionecrosis are greater than in any other organ with the exception of the esophagus. If treated carcinomas become necrotic when situated in the skin, mouth or other locations they are accessible to treatment, but radionecrosis of the gastric wall may lead to a fatal hemorrhage. perforation causing peritonitis or perforation into another abdominal organ, such as the colon, with a resultant gastrocolic fistula.

The removal of a biopsy specimen for microscopic study of the tumor and an evaluation of its radiosensitivity and histologic grading is an important preliminary step in the radiation treatment of most cancers. It is difficult to obtain this tissue from gastric cancer except by laparotomy or occasionally by gastroscopy.

#### INDICATIONS FOR AND ADVANTAGES OF IRRADIATION IN THE TREATMENT OF CANCER OF THE STOMACH

Irradiation is not proposed as a substitute for resection of the stomach with cancer in an operable stage. Its chief indication is in the treatment of gastric cancers classified as inoperable because of the extent of the disease or because of some particular location of the tumor such as in the cardia or the fundus. As inoperable gastric cancers are inevitably fatal if untreated, nothing has been lost by the institution of radiation therapy under these circumstances.

The surgeon occasionally sees a patient with an apparently operable gastric cancer who will not consent to any operative procedure or whose physical condition will not permit radical surgical procedures. In such situations the only recourse left has been to attempt palliative irradiation. Although the technical and biologic handicaps to the successful irradiation of gastric cancer are so numerous, it seems that considerable experimentation in the methods of irradiation may surmount these difficulties in part.

Like other organs, the stomach has its quota of radiosensitive carcinomas, although this type is not relatively as frequent in the stomach as in the tonsil, cervix and lymphoid tissues. It is estimated that less than 10 per cent of gastric cancers may be classified as radiosensitive. but a greater percentage will respond in some degree to well planned radiation therapy.

Obstructive inoperable carcinomas of the cardia and pylorus are best treated by such palliative operations as gastrostomy and gastrojejunostomy, respectively, but when these are contraindicated by the patient's age or physical condition or when one fails to obtain consent for operation, radiation therapy has, in some cases, given temporary relief from the obstruction. This improvement is estimated clinically by the patient's ability to swallow solid food if the cardia is involved or by the diminution in the retention of gastric residue after six and twenty-four hours, as observed in roentgenograms made after the ingestion of a barium sulphate meal. If these short-circuiting operations are possible, they are followed by irradiation as a supplementary palliative procedure.

In the published operative statistics from various hospitals one observes quite frequently the great proportion of exploratory laparotomies which are done for inoperable carcinomas of the stomach. In such cases the surgeon is content with ascertaining the extent of the growth and possibly with securing a biopsy specimen. Under such circumstances it does not entail much additional risk to treat an inoperable carcinoma at this time with radium applied interstitially. No surgeon could be censured for the use of radium under these conditions.

#### RADIOSENSITIVITY OF GASTRIC CANCERS

The majority of cancers of the stomach are radioresistant, less than 10 per cent exhibiting clinical improvement and roentgenographic evidence of regression following moderate exposure to external irradiation. As we shall point out later, the most radiosensitive gastric cancers are located in the cardia and the fundus.<sup>24</sup> Our experience has not been sufficient to identify with certainty the radiosensitive varieties of gastric cancer, but we have empirically formulated some opinions based on the gross anatomic classification of Ewing.<sup>25</sup> The bulky adenocarcinoma is a circumscribed sessile fungating tumor occasionally developing from an adenomatous polyp. When situated at the cardia or in the fundus, this tumor may partially regress following external irradiation, although it is more prone than most tumors to undergo necrosis and deep ulceration with consequent hemorrhage or perforation. The rare subgroup of villous tumors (papillary adenoma malignum) is composed of well developed branching vascular papillae (fig. 1) which shrink following radiation therapy by a process of obliterative vascular changes and infarction.

24. Stewart, F. W.: Radiosensitivity of Tumors, *Arch. Surg.* **27**:979 (Dec.) 1933.

25. Ewing, J.: *Neoplastic Diseases*, ed. 3, Philadelphia, W. B. Saunders Company, 1928; footnote 3d.

The gelatinous carcinoma of the stomach, like its congeners in other organs, is endowed with the same degree of radioresistance as the normal stomach, or a greater degree. All varieties of gelatinous carcinoma, including the infiltrating signet-ring cell type, are composed of well differentiated adult cells in a gelatinous stroma, which constitutes a tissue bed most unfavorable to changes produced by irradiation.



Fig. 1.—Papillary adenoma malignum of the stomach, of grade 1 and radio-sensitive.

Furthermore, the gelatinous cancer penetrates the gastric wall early and widely involves the peritoneum, thus offering a further handicap even to palliative irradiation.

Ewing<sup>26</sup> predicted that we would occasionally discover a radio-sensitive ulcerocancer, and his prophecy has been verified by an astonishing regression and palliation in two histologically verified cases in

26. Ewing, J.: Radiosensitivity, *Radiology* 13:313, 1930.

which the tumor was treated by intensive external irradiation (case 3). The carcinomatous ulcer is usually a small alveolar cancer and possesses none of the histologic earmarks tokening radiosensitivity.

The carcinoma telangiectatica is a large, round, circumscribed ulcerating tumor occurring chiefly in the fundus and the cardia. It is the type of medullary cancer or carcinoma simplex often associated with

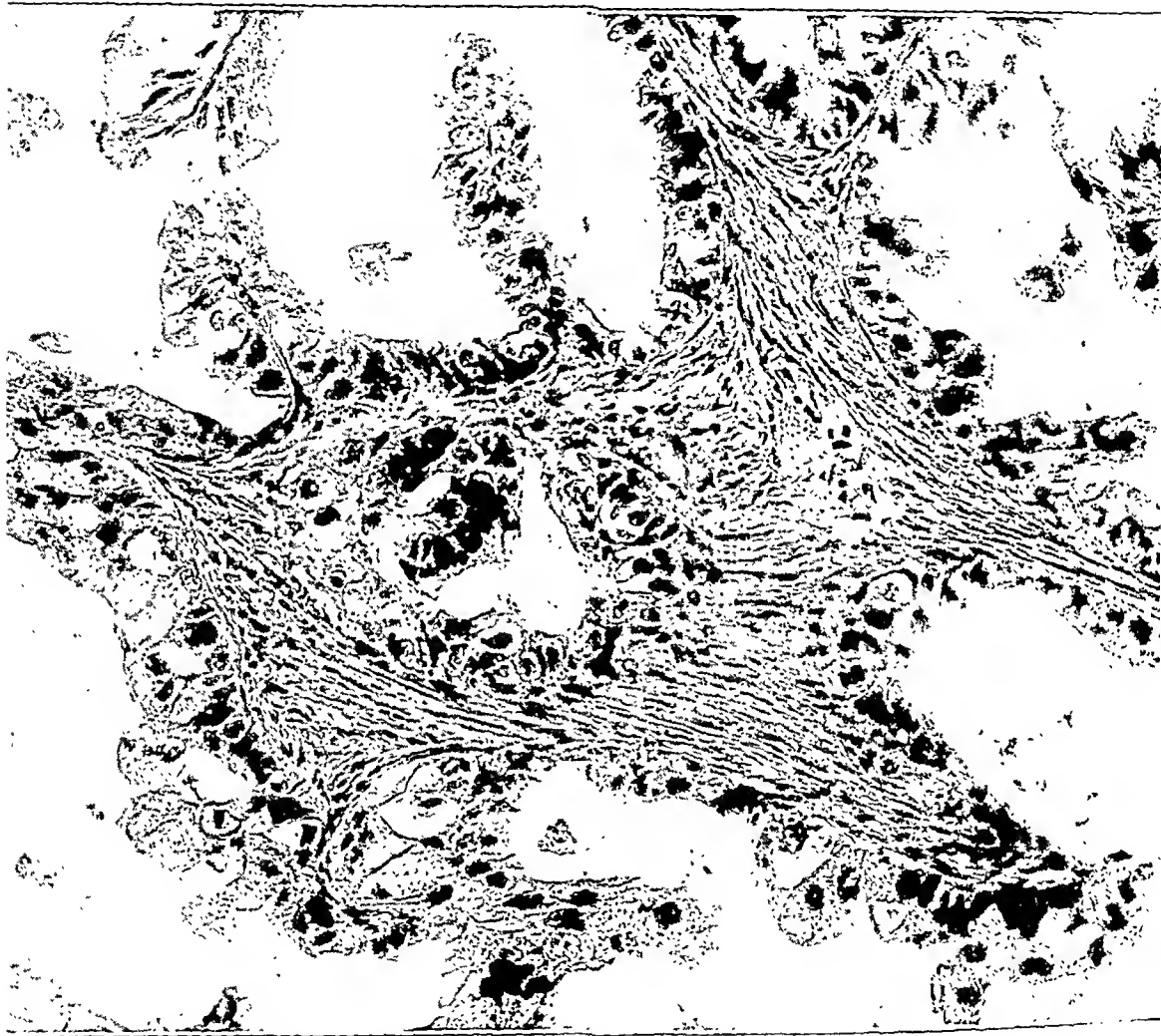


Fig. 2.—Papillary adenoma malignum of the stomach, of grade 2 and radio-resistant.

profound anemia because of continuous or intermittent hemorrhages. We have had several patients with this type of carcinoma who have been decidedly improved by roentgen or radium treatment (case 2 and 4).

Ewing<sup>27</sup> has observed that the small cell cancers originating from the base of the gastric glands constitute a radiosensitive group. There

27. Ewing, J.: Tissue Reactions to Radiation, *Am. J. Roentgenol.* **15**:93, 1926; Factors Determining Radioresistance in Tumors, *Radiology* **14**:186, 1930.

is a certain anaplastic small cell gastric cancer which bears a close morphologic resemblance to lymphosarcoma and is sensitive to irradiation. Such a tumor may be entirely lacking in desmoplastic properties and extend diffusely as a small alveolar or solid tubular growth over the mucosa or intramurally.



Fig. 3.—Adenoma malignum of the cardiac orifice, of grade 2 and radio-resistant. There is considerable lymphocytic infiltration of the stroma.

The diffuse scirrhous carcinoma (linitis plastica type) and fibrocarcinoma are by their very nature unresponsive to irradiation. The opposite extreme in radiosensitivity is the rare primary lymphosarcoma of the stomach. One of our patients with an inoperable sarcoma of this type from which a biopsy specimen was obtained is now living six years after treatment by the radium element pack (case 1).



## PREPARATION OF THE PATIENT FOR RADIATION THERAPY

If a patient is to be subjected to irradiation the stomach should not contain food at the time of treatment. This is secured either by control of the diet during the period of treatment or by using liquid and semi-solid food that rapidly leaves the stomach. Another valuable adjunct



Fig. 4.—Superficial adenoma malignum of the stomach with gelatinous degeneration. There are multiple foci of origin visibly continuous with normal gastric glands. The adjoining mucosa is the site of hypertrophic gastritis.

is the use of gastric lavage. The patient should have the same careful preparation as for operation on the stomach, although not so arduous. Gastric lavage is useful to remove residue and to lessen the infection of an open ulcerated carcinoma. Lavage should be continued daily if

possible until the gastric contents remain clean. This is essential, as infection constitutes a dangerous risk for radiation therapy for two reasons: (1) Irradiation increases the amount of necrosis of the tumor and permits infection to gain headway, and (2) in the presence of

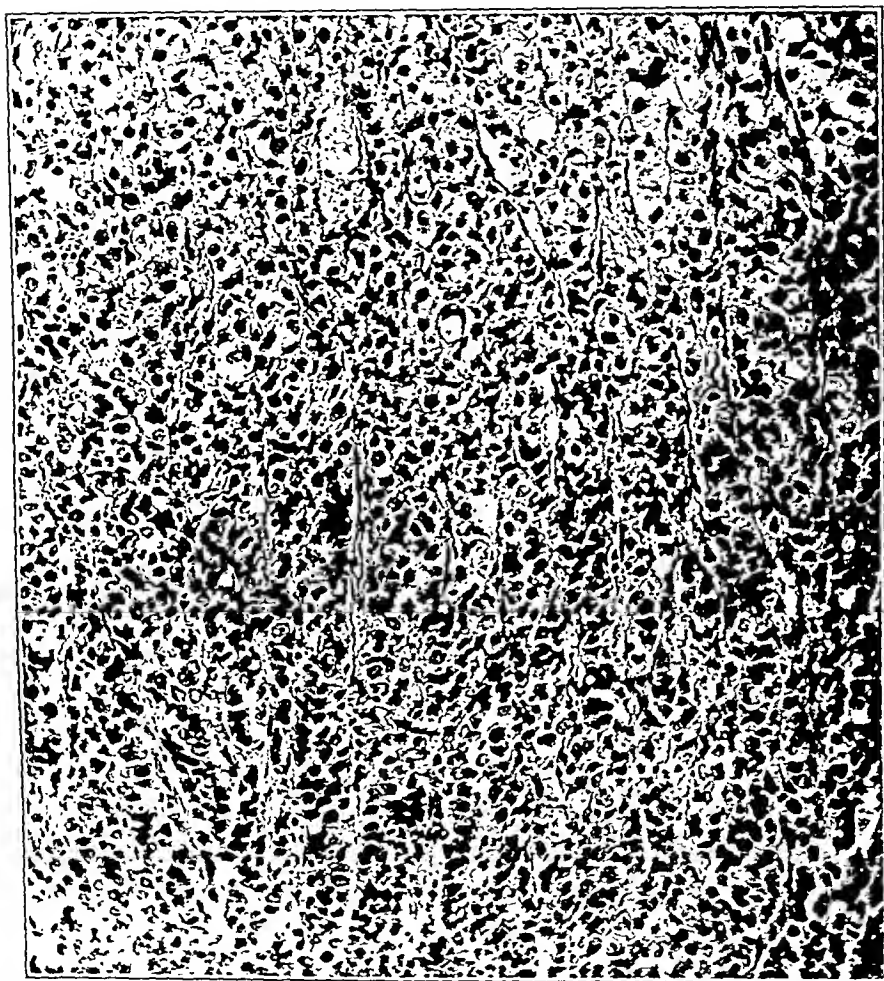


Fig. 5.—Diffuse tubular superficial carcinoma of the stomach, of grade 3 and radiosensitive. It involves the entire gastric mucosa in all subdivisions of the stomach.

infection irradiation may lead to such massive necrosis that hemorrhage occurs.

When external irradiation is employed, it should be given in the morning. During the remainder of the day the patient is limited to a liquid or semisolid diet, which is of high caloric content and is well

balanced. Because of the close proximity of the liver and pancreas to the stomach the patient suffers greatly from the immediate constitutional reaction following external irradiation. One of the best means to combat this reaction is to insure an abundant intake of fluid, such as water in large quantities, orange juice strained through a cloth, grapefruit juice, ginger ale, etc. If insufficient fluid is given by this means it may

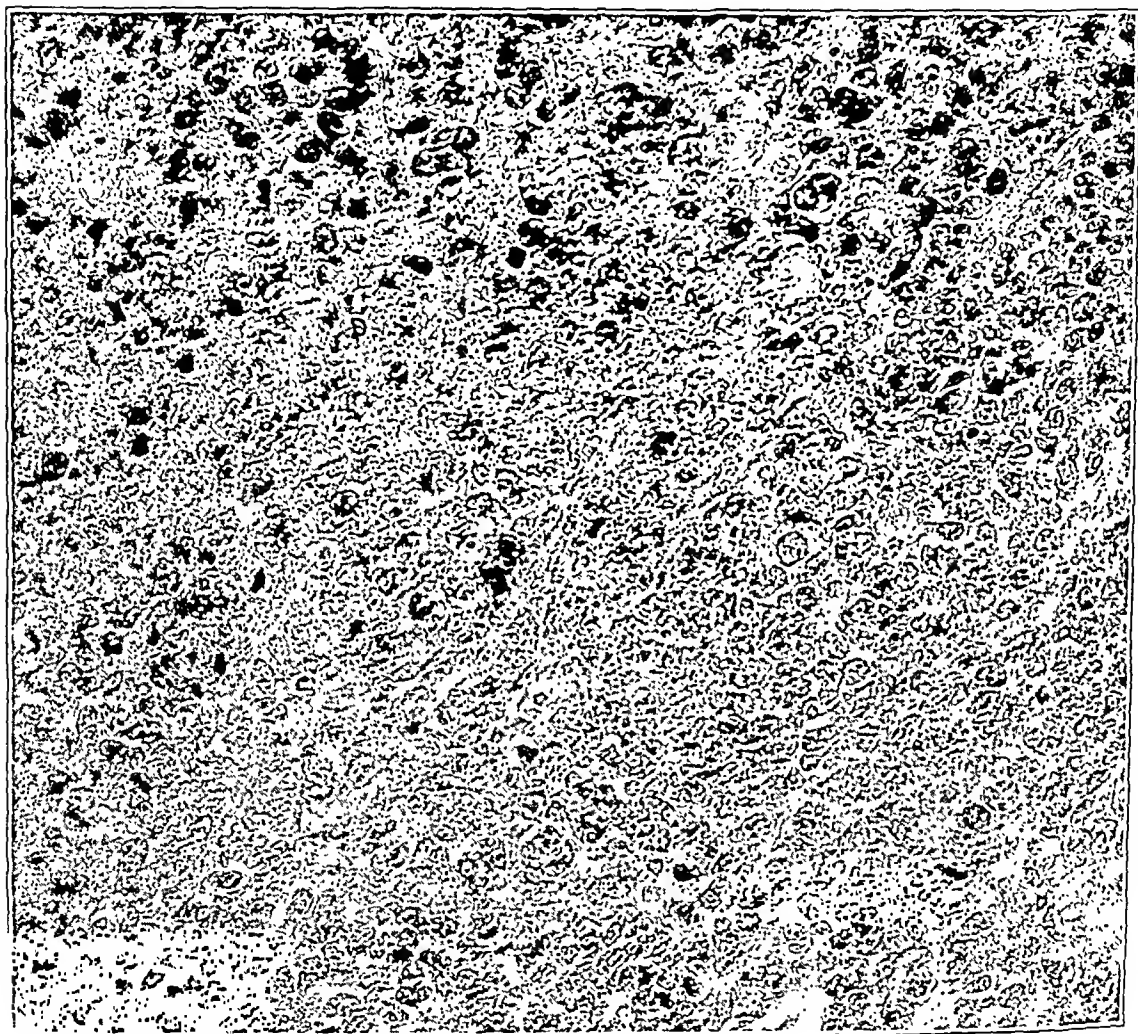


Fig. 6.—Cellular anaplastic carcinoma of the stomach. There is insufficient differentiation of this carcinoma to identify it as of gastric origin. The anaplasia, numerous mitoses, absence of desmoplasia and hyperchromatism of the nuclei indicate that this carcinoma is radiosensitive.

be necessary to supplement the fluid intake by hypodermoclyses of physiologic solution of sodium chloride or by intravenous infusions of dextrose solution. The cause of radiation sickness is probably the partial depletion of glycogen in the liver; therefore, the administration of dextrose intravenously as well as candy by mouth, if tolerated, is a

rational procedure. Other methods helpful in combating radiation sickness are: the administration of sodium bicarbonate after meals and the use of viosterol (from 8 to 10 drops daily), tomato juice twice daily and calcium lactate by mouth.

The patient undergoing roentgen or radium treatments should not work but should rest a considerable part of the day. The mouth should be cleaned and infected teeth cared for in order to avoid infection of the gastric carcinoma. If the patient is anemic it is most essential to give one or more blood transfusions. The advantages of this are several. It increases the strength and vigor of the patient, it enables him to tolerate the rigor of intensive irradiation, and it contributes in some intangible way to a more effective irradiation of the tumor or rather to a better response of the tumor to irradiation.

#### PHYSICAL FACTORS IN THE RADIATION THERAPY OF GASTRIC CANCER

The action of radiation in causing regression of the tumor is generally conceded to be a direct effect on the tumor cells themselves and on the tissue immediately surrounding them. This means that the only radiation which is effective is that which reaches the region of the growth. In order to practice radiation therapy to the best advantage, therefore, it is essential to find out how much radiation may be expected to produce a given effect and then to devise means for delivering this quantity to the tissues in question.

It is usually true that different points in an irradiated mass do not receive the same amount of radiation; this is inevitable when interstitial sources are used. If regression of the tumor depends on every point receiving at least a definite quantity, then it is necessary to know the minimum dose delivered at any point within the lesion. This is the tissue dose referred to in the discussion on radiation therapy. It is of interest to know the amount of radiation leaving the source, because, other things being equal, the more powerful the source the shorter the time of treatment. It is important to know the quantity falling on a given skin area, since skin tolerance limits the dose which can be given through any one field. Neither of these, however, is of much value without the knowledge of the amount actually reaching the diseased cells.

For the expression of quantity it is necessary to adopt a unit. Various units have been proposed for measuring "doses" of radiation; none of them is very satisfactory, and none has been officially adopted. At the Memorial Hospital the unit is the so-called "threshold erythema dose" (T.E.D.), defined as the amount of radiation which, administered at a single exposure, will produce a visible tanning or reddening of the

skin in from two to four weeks' time in 80 per cent of the cases and no visible effect in the others. This dose can be determined experimentally for any given type of radiation with considerable accuracy. The roentgen, which is the accepted unit for specifying the output of the x-ray tube, is not suitable for expressing tissue doses. By definition it is a quantity of radiation measured by an effect produced in air under specified conditions. It is at present established only for the roentgen rays generated within a certain range of voltage; it has not been satisfactorily extended to very high voltage roentgen rays or to the gamma rays of radium. Moreover, when the measuring instrument is placed on or in a mass of matter, in addition to the direct or primary beam of radiation, it is affected by the rays scattered into it from the surrounding substances. The relative amount of this "back scatter" under conditions of therapy has not been satisfactorily determined. Since the scattered radiation is automatically included in the erythema dose when it is determined experimentally, this difficulty does not arise when that unit is used.

For the measurement of radiation within the tissues, no direct method is at present available. In order to obtain approximate values, it is necessary to make certain assumptions, based on the results of experiments performed outside the body. The most common method is to determine, with a small ionization chamber, the intensity of radiation on the surface of a tank of water (a so-called water phantom) and the relative intensities at various depths. It is then assumed that in a volume of tissue comparable to that of the phantom, with the same beam of radiation, the intensities at various levels will be the same as those in the water. Thus, if the ionization measurements indicated at a depth of 10 cm. an intensity of 33 per cent of that on the surface, it is assumed that if 1 threshold erythema dose falls on the skin, one third of a threshold erythema dose is delivered at a depth of 10 cm. This would be true if the quality of radiation remained the same. As a matter of fact, it is altered somewhat in its passage through matter, and after it has traversed several centimeters the change may be considerable. The action of this changed (less penetrating) radiation may be different in the production of ionization and of erythema. There is some evidence to show that for 200 kilovolts roentgen rays the difference is not great, so that the assumption in this case would be justified. With gamma rays from external sources, on the other hand, the difference may be considerable; there are at present few data on which to base an opinion.

It is also necessary in discussing physical measurement of the dosage of radiation to emphasize the importance of the time factor. This is not a physical factor and is not taken account of by physical measure-

ments. Laboratory instruments if sufficiently sensitive will register the same total effect from a given quantity of radiation whether it is administered all at once or subdivided in any of the ways customary in clinical irradiation. The biologic response under these different conditions, however, may vary a great deal. This should be borne in mind in connection with any discussion of tissue dosage.

There are two methods by which radiation may be delivered to a malignant growth within the body. In one, the source of the roentgen rays is external—either an x-ray tube or a radium applicator such as the large pack. From such a source the rays must pass through skin and other normal structures before they reach their objective. In the other, the source consists of one or more small tubes or needles containing radioactive material, introduced directly into the growth or the region immediately surrounding it. In this case, the rays arrive at the diseased tissues without having first to traverse normal ones.

These two methods will be considered somewhat in detail, particularly with regard to their applicability to treatment of cancer of the stomach. In the first, a beam of the roentgen rays or gamma rays will be directed toward the region of the body which is, as nearly as can be determined, directly over the lesion. If the mass is situated, for example, 10 cm. below the surface of the body, these rays must then traverse 10 cm. of tissue before they arrive at the malignant growth. In doing so, a considerable proportion of them will be absorbed or scattered from their direct route.<sup>28</sup> Also, because the beam spreads as it advances, less radiation will fall on a unit area 10 cm. below the surface than on a unit area on the skin. For all these reasons, with the usual x-ray set-up employed in the treatment of gastric carcinoma or with the large radium pack used under the most favorable conditions, only about one third of the radiation incident on the skin reaches a depth of 10 cm. It is possible by increasing the filter, by increasing the target skin distance or by increasing the field to increase the relative depth dose somewhat, but with the facilities generally available at present it cannot be brought up to more than one half of the skin dose in any practicable manner. Moreover, it must not be lost sight of that increases produced by the first two of these methods are very uneconomical. By increasing the filter in the x-ray beam from 0.5 mm. of copper to 2 mm. of copper, the dose at a depth of 10 cm. can be increased about 6 per cent, but the intensity of the beam is so much decreased by this additional filter that an exposure almost three times as long is required to deliver the same dose on the

28. Lee, B. J.; Pack, G. T.; Quimby, E. H., and Stewart, F. W.: Irradiation of Mammary Cancer with Special Reference to Measured Tissue Dosage, *Arch. Surg.* **24**:339 (March) 1932.

skin. Increasing the target skin distance from 50 to 70 cm. increases the depth dose by about 10 per cent but doubles the time of irradiation necessary to deliver a given skin dose. It is clear, then, that there is an economic limit to gains in depth dosage obtained by such means. Increasing the size of the field from 10 by 10 cm. to 20 by 20 cm. increases the dose at 10 cm. depth by about 20 per cent. This appears desirable, but it should be noted that a large part of the vital organs, which may be partly avoided with a small beam, will inevitably receive doses of radiation, in some cases greater than that delivered to the tumor. Some of these organs are quite radiosensitive and should be protected if possible.

There remains the method of increasing the depth dose by irradiating through more than one area—the method of “cross-fire.” If the lesion is situated about half-way through the body, the use of a posterior field directly opposite the original anterior one will double the dose delivered at the growth. The use of lateral fields in addition would increase the dose still more, but this procedure is open to the same objection as the increase in size of the anterior and posterior fields, namely, the increased irradiation of normal organs.

All that has just been said about relative depth doses holds true no matter what quantity of radiation is delivered on the skin. If one erythema dose is delivered to an anterior and a posterior field, with an abdomen 20 cm. in diameter, the region in the middle will receive two thirds of an erythema dose, one third from each field. If each area receives only one half of an erythema dose, the central region gets a total of two sixths of an erythema dose. When daily doses of radiation as small as this are given they may be repeated without permanent injury to the skin, until a great deal more radiation has been given than would be possible with a single treatment. If one half of an erythema dose is given daily, anterior and posterior fields being irradiated on alternate days, it is possible to give as many as several erythema doses per skin field. But the same proportion holds, and the tumor at the center will receive just two thirds as much as a skin field.

Four erythema doses subdivided in this manner will not produce much more reaction in the skin than 1 erythema dose delivered at a single exposure. It is, therefore, not obvious that two and two-thirds erythema doses delivered into the tumor during this treatment will produce a more marked effect than two thirds of an erythema dose delivered from two single exposures. From a purely physical point of view it would not be expected to. Interestingly enough, in clinical experience with some types of neoplasm, the larger dose, divided over a number of treatments, does produce a more marked effect on the tumor than the single smaller one. It seems that this must be due to a difference in the rate of recuperation between the normal and the diseased

cells. The normal cells recover well from the effects of the partial dose, so that the next treatment finds a fairly healthy cell. The tumor cells, on the other hand, do not recover so well, and the next dose of radiation falls on a partially disabled cell. If the reverse were true and the malignant cells recovered more quickly than the normal, then the single intense irradiation would be the method of choice. If the rates of recovery were the same, the subdivision of irradiation would make no difference. It is only by experience in the treatment of each type of disease that the best method for different lesions can be determined. It cannot be assumed that because one growth in one part of the body responds well to a given sort of treatment any other type will behave in the same manner.

Even with the advantage gained by divided and protracted treatment in favorable cases, the quantity of radiation which it is possible to deliver by external irradiation to the average lesion of the stomach within a reasonable period of time is considerably less than that which has been found necessary to produce regression of squamous carcinoma in other parts of the body. Figures 7 and 8 show the distribution of radiation throughout the upper portion of the abdomen in percentages of the amount falling on the skin for the two types of external irradiation most commonly used in gastric cancer.<sup>29</sup> In figure 7 the roentgen rays generated at a 200 kilovolt peak, filtered through 0.5 mm. of copper and 2 mm. of aluminum, with a target skin distance of 50 cm., fall on single anterior and posterior fields of 100 sq. cm. each. In figure 8 the radium element pack, with a skin distance of 15 cm., irradiates the same regions. The field for this set-up cannot be limited to 100 sq. cm., nor can it be exactly defined. From these diagrams it is seen that when one threshold erythema dose (100 per cent) falls on each of these two skin fields, as was previously stated, about two thirds of an erythema dose will be delivered throughout the region of the stomach. A possible total of six threshold erythema doses per field, delivered within one month, would deliver about four threshold erythema doses to the lesion.

In certain cases it may be possible to supplement external irradiation by the second method mentioned, the interstitial implantation sources. For rather small, accessible circumscribed lesions, this type of treatment seems to be ideal. The radiation is delivered exactly where it is needed; the tumor cells receive more than the normal ones; unaffected organs are, in general, far enough away not to be damaged, and the general or constitutional reaction is minimized.

<sup>29</sup> Quimby, E. H., and Pack, G. T.: The Skin Erythema for Combination of Gamma and Roentgen Rays, *Radiology* 13:306, 1929; Further Studies on the Skin Erythema with Combinations of Two Types of Radiation, *ibid.* 15:30, 1930.



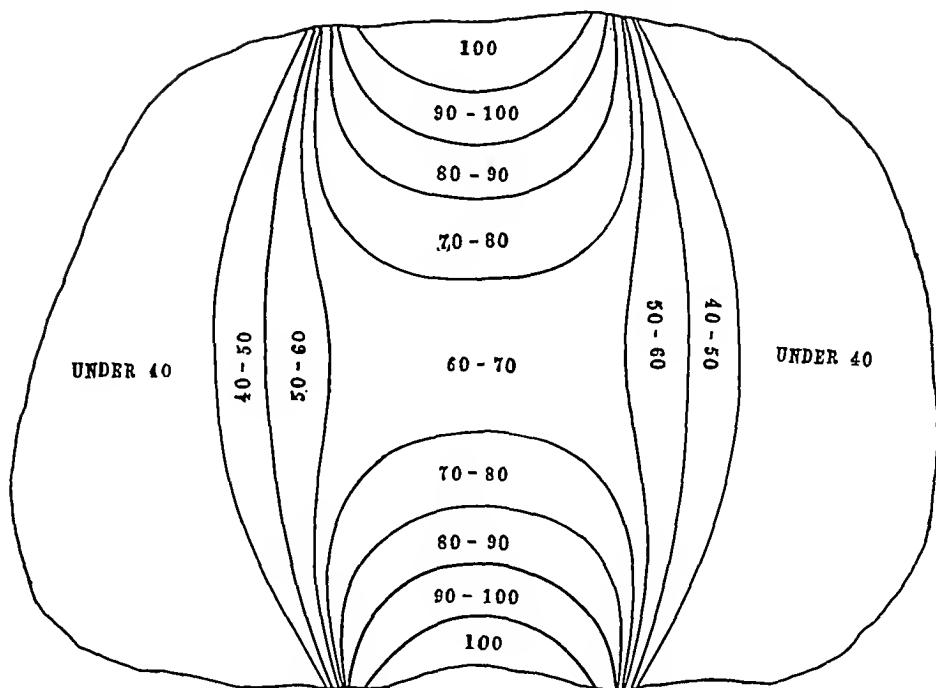


Fig. 7.—Cross-section of the body at the level of the pylorus showing the distribution of radiation from the x-rays. The factors of treatment are: 200 kilovolt peak; 0.5 mm. copper filter; 50 cm. target skin distance, and 10 by 10 cm. anterior and posterior fields.

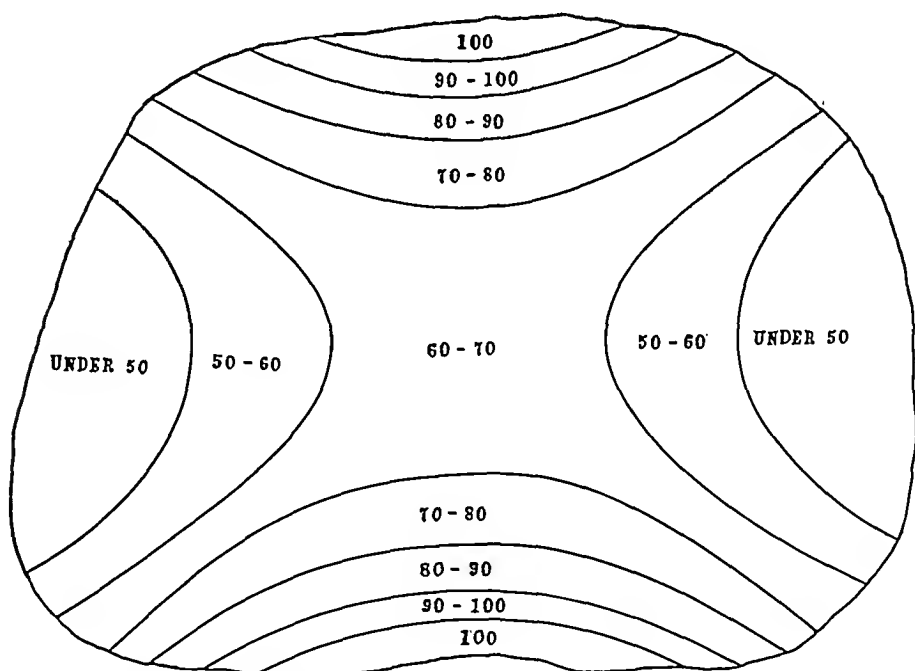


Fig. 8.—Cross-section of the body at the level of the pylorus showing the distribution of radiation from a radium element pack. A filter equivalent to 2 mm. of lead is used. The anterior and posterior fields are irradiated at a skin distance of 15 cm.

A great deal of information is now available as to the best method of delivering the desired dose by means of interstitial irradiation.<sup>30</sup> It is necessary to take into account the type of sources to be used and the size and shape of the lesion. Sources may be permanent radon seeds, removable radium or radon seeds or removable radium or radon needles of various lengths. As far as the radiation emitted by these various implants is concerned, there is little choice. The beta and gamma rays from radium and radon are identical. Filtration should always be at least 0.25 mm. of gold or platinum or its equivalent; beyond this, increase is not important. For globular or disk-shaped lesions it is probably easier to get fairly uniform irradiation by means of seeds; for elongated or infiltrating growths long needles may be preferable. At the Memorial Hospital interstitial irradiation for gastric

TABLE 1.—*Millicuries in Gold Seeds Required to Deliver Specified Doses to Masses of Various Diameters*

Skin Erythema Doses	Diameter of Mass, Cm.											
	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.0	6.0	7.0	8.0
	Number of Millicuries											
1	0.2	0.5	0.8	1.5	2.0	2.4	2.9	3.4	4.0	5.4	7.0	9.0
2	0.4	1.0	1.6	3.0	4.0	4.8	5.8	6.8	8.0	11	14	18
3	0.6	1.5	2.4	4.5	6.0	7.2	8.7	10	12	16	21	27
4	0.8	2.0	3.2	6.0	8.0	9.6	12	14	16	22	28	36
5	1.0	2.5	4.0	7.5	10	12	14	17	20	27	35	45
6	1.2	3.0	4.8	9.0	12	14	17	20	24	32	42	54
7	1.4	3.5	5.6	10	14	17	20	24	28	38	49	63
8	1.6	4.0	6.4	12	16	19	23	27	32	43	56	72
9	1.8	4.5	7.2	14	18	22	26	31	36	49	63	81
10	2.0	5.0	8.0	15	20	24	29	34	40	54	70	90
11	2.2	5.5	8.8	17	22	26	32	37	44	59	77	99
12	2.4	6.0	9.6	18	24	29	35	41	48	65	84	108
13	2.6	6.5	10	20	26	31	38	44	52	70	91	117
14	2.8	7.0	12	21	28	34	41	48	56	76	98	126
15	3.0	7.5	13	23	30	36	44	51	60	81	105	135

carcinoma has been carried out with gold radon seeds. For purposes of calculating the dosage, the lesions are considered as spheres or groups of spheres. Table 1 shows the amount of radon necessary to deliver specified doses within masses of given sizes or, conversely, the tissue doses resulting from the implantation of certain quantities of radon. The doses given are the minimum delivered within the specified volume, when the seeds are uniformly distributed within the inner half of the radius of the specified sphere.

It should be mentioned that any attempt to irradiate adequately a very large mass by interstitial sources may necessitate the use of more radiation than will be tolerated by the organism as a whole. The amount which can be thus tolerated is a matter for clinical determination.

30. Quimby, E. H.: The Intensity of Radiation in the Vicinity of Filtered Radon Implants, *Radiology* 10:365, 1928.

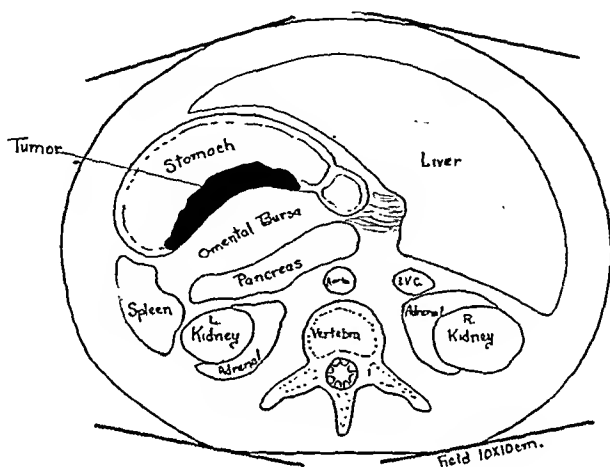
## EXTERNAL IRRADIATION OF GASTRIC CANCER

The effectiveness of external irradiation depends not only on the degree of radiosensitivity of the gastric cancer but also on the depth dose or tissue dose delivered to the tumor within a certain time. The depth dose is modified by certain factors, as we have already explained, such as the source of radiation (200 kilovolt roentgen rays, 700 kilovolt roentgen rays and gamma rays from a radium element pack), the thickness and quality of the filter, the target skin distance and the target tumor distance. If all the factors of treatment are equal, it is seen that the dose delivered must vary according to the size of the patient, i. e., his body thickness. The estimation of this dosage is aided by a correct measurement with calipers of each patient while he is in the recumbent posture. The lateral and anteroposterior diameters of the body at the level of the epigastrium are recorded. Representative cross-section charts of the body at all the levels of the stomach are available and may be projected to a size comparable with each patient's measurements. The exact location and approximate size of the carcinoma are drawn on these topographic outlines, so that the computation of depth dosage may be done graphically and accurately (figs. 9, 10 and 11).

All external irradiation is given while the patient is recumbent in the lateral, prone or supine position. Prior to the institution of treatment, fluoroscopy after ingestion of a barium meal is done in each of these three positions in order that the exact position of the tumor might be projected and recorded in indelible ink on the patient's skin. The skin portals for irradiation are centered over these markings so that the beams of radiation are properly directed to cross-fire at the tumor. Four ports, right and left anterior and posterior, have been used for carcinomas in the distal segment of the stomach, but since we have found that nearly all our satisfactory therapeutic results are for carcinomas of the cardia and the fundus we seldom have occasion to employ these fields. Carcinomas of the proximal segment of the stomach are treated through three ports in the upper left quadrant of the abdomen (anterior, lateral and posterior) unless the patient is obese, when as many as five ports may be used to circumirradiate the left half of the abdomen. These ports measure 12 by 14 cm. or more.

The different modalities employed for external irradiation may be briefly described. We have found it worth while to apply the 200 kilovolt roentgen rays at a distance of 70 cm. rather than at 50 cm., although this set-up requires twice the time of irradiation to deliver the same dose to the skin. The increased time of each treatment is an advantage in our opinion, and, furthermore, the depth dose reaching the tumor is slightly increased. The filter commonly used is 0.5 mm. copper and 2 mm. aluminum. The depth dose is augmented considerably by

increasing the target skin distance to 150 cm., which we have done in several instances, with notable results in two cases (case 3). The roentgen exposure necessary to deliver a specified dose at this distance is nine times as long as with a target skin distance of 50 cm. We have used circular anterior and posterior skin ports at this distance measuring 27 cm. in diameter.



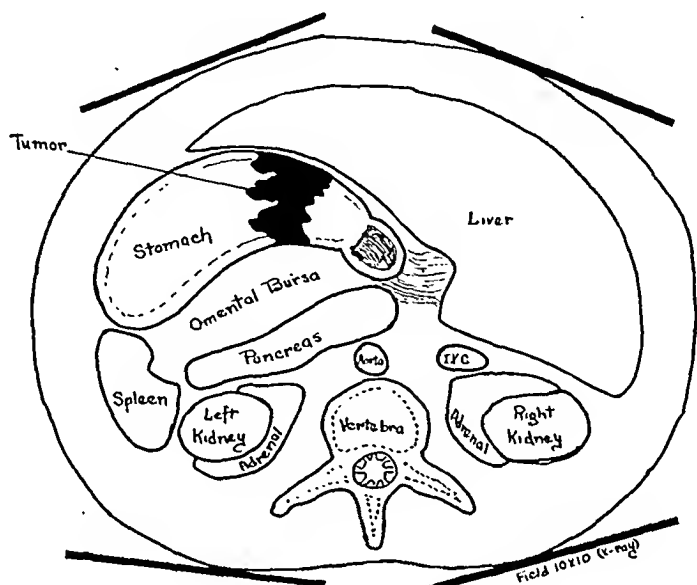
### HIGH VOLTAGE X-RAY

Region	Dose to Skin Total r.	TED	Dose to Tumor Total Depth	TED
Left Epigastrium Ant.	840	1.4	55	0.7
" " Rot.	840	1.4	35	0.5
Right " Rot.	840	1.4	20	0.3
" " Ant.	840	1.4	25	0.3
Stomach Ant.	1000	1.7	30	0.5
Stomach Post.	500	0.8	50	0.4
Total Threshold Erythema Doses = 2.7				

Fig. 9.—Cross-section measurement of a patient with gastric cancer, illustrating the computation of depth dosage of radiation.

We have treated some patients with the General Electric 700 kilovolt x-ray machine, using a distance of 60 cm. and a filter equivalent to 5 mm. of copper. The depth dose with this set-up is not quite as great as that obtained with the 200 kilovolt x-ray machine at a distance of 150 cm., but the roentgen rays are of shorter wavelength because of the heavier filter. The threshold erythema dose for the 700 kilovolt roentgen rays with 5 mm. copper filter is 700 roentgens, whereas for the 200 kilovolt roentgen rays with 0.5 mm. copper plus 2 mm. aluminum

it is 525 roentgens, indicating that the skin and normal tissues are considerably more tolerant for the roentgen rays of shorter wavelength. We have experimental evidence to indicate that cancer and other rapidly growing tissues are not more tolerant of these ultrashort roentgen rays; hence in treatment we may take advantage of this differential sensitivity of tumor and normal tissues.



### HIGH VOLTAGE X-RAY

Region	Dosage to Skin Total r.	T.E.D.	Dosage to Tumor % at Depth	T.E.D.	
L. Abd. Ant.	762	1.3	30	0.4	
L. " Post.	762	1.3	15	0.2	
R. " Post.	762	1.3	60	0.8	
R. " Ant.	762	1.3	25	0.3	Total 1.7

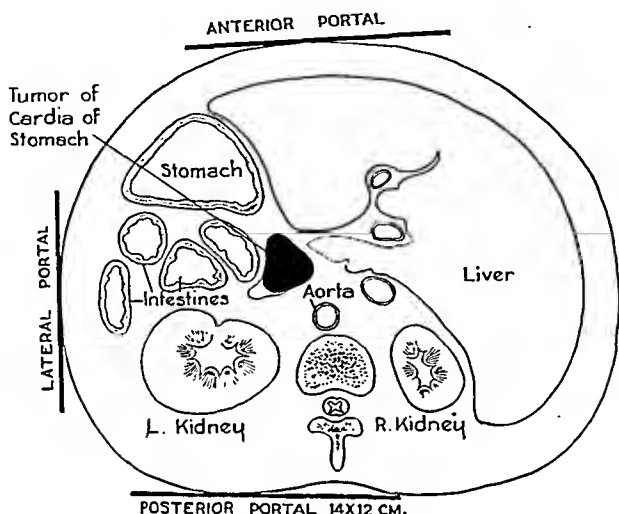
### RADIUM ELEMENT PAGK

Region	Mg.-hrs.	T.E.D.	% at Depth	T.E.D.	
Abdomen Ant.	75,000	1.25	50	0.6	
" Post.	75,000	1.25	25	0.4	Total 1.0
Total to Tumor by all radiation = 2.7 T.E.D.					

Fig. 10.—Cross-section measurement of a patient with gastric cancer, illustrating the computation of depth dosage of radiation.

The first patients treated were given doses of from 750 to 800 roentgens to each skin portal, with a repetition of this intensive cycle in from ten to twelve weeks. The tissue dose administered to the tumors by this technic was inconsiderable. The present system of roentgen therapy depends on the daily administration of only from 300 to 350 roentgens to one skin port, alternating on subsequent days with treatments of similar dosage to the other ports, until each area of skin

receives a total of 3,000 roentgens. The daily fractionated treatments therefore consume the better part of a month for their completion. Coutard first advocated this principle in the treatment of cancer of the pharynx and larynx, and it has since proved its worth in cases of cancer of the breast and uterus. The patients are better able to tolerate these smaller daily treatments, and the tissue dose to the tumor is greatly augmented.



#### HIGH VOLTAGE X-RADIATION

Region	Dose to skin Total r	T.E.D.	Dose to tumor % of depth	T.E.D.
Stomach Ant.	3000	5.4	35	1.89
" Lat.	3000	5.4	25	1.35
" Post.	3000	5.4	35	1.89
Total Threshold Erythema Doses				5.13

#### INTERSTITIAL RADON GOLD SEED

Region	Number of seed	Total mc.	T.E.D.
Tumor of Cardia	22	30	5
Total T.E.D. to Tumor = 10			

Fig. 11.—Cross-section measurement of a patient with gastric cancer, illustrating the computation of depth dosage of radiation.

Our 4 Gm. radium element pack has proved to be our most effective external applicator, although certain factors in treatment, such as the skin distance and the time of irradiation, are not altogether satisfactory. The filter is 0.3 mm. of platinum and 1.5 mm. of brass. The skin distance is 15 cm., and the dose at this distance is from 80,000 to 100,000 milligram hours (from 80 to 100 gram hours). Each daily treatment consists of two hours' exposure so that from twenty to thirty days in

all are required to complete the cycle of irradiation. We have the distinct clinical impression that with tissue doses of comparable degree the radium element pack is superior to our other modes of external irradiation (fig. 12).

Isodosis curves have been prepared with the use of water phantoms and cadavers; the depth dose actually delivered to the gastric cancer may be estimated from these curves. This dose is expressed in terms of threshold erythema units. We have been able to deliver from three

TABLE 2.—*Comparison of Depth Doses Delivered by Three Sources of Radiation*

Settings in Use at Present											
Depth, Cm.	200 Kv. X-Rays 50 Cm. Distance 0.5 Mm. Cu. and 2 Mm. Al.				700 Kv. X-Rays 60 Cm. Distance 5 Mm. Cu.				Gamma Rays		
									10 Cm.	15 Cm.	
	50 Sq.Cm.	100 Sq.Cm.	200 Sq.Cm.	400 Sq.Cm.	50 Sq.Cm.	100 Sq.Cm.	200 Sq.Cm.	400 Sq.Cm.	100 Sq.Cm.	150 Sq.Cm.	
0	100	100	100	100	100	100	100	100	100	100	
2	77	82	84	85	78	82	85	86	67	76	
5	49	51	57	60	53	58	63	66	40	51	
10	21	25	28	31	26	30	34	38	20	29	
15	8	10	12	14	13	16	19	22	14	17	
T.E.D. Time	Minutes				Minutes				Hours		
Water	9.0	8.3	7.8	7.1	48	44	41	39	7.5	15	
Air	65	60	56	53							
Other Possible Settings											
Depth, Cm.	200 Kv. X-Rays (0.5 Mm. Cu., 100 Sq. Cm.)				Gamma Rays						
	70 Cm. Dist.	85 Cm. Dist.	100 Cm. Dist.	150 Cm. Dist.	20 Cm.	25 Cm.					
0	100	100	100	100	100	100					
2	84	85	85	87	81	83					
5	56	58	59	62	58	63					
10	27	29	30	32	35	40					
15	11	12	13	14	22	26					
T.E.D. Time	Minutes				Hours						
Water	16	24	33	75	26	44					
Air	120 (2 hr.)	180 (3 hr.)	240 (4 hr.)	540 (9 hr.)							

to five threshold erythema doses to carcinomas of the stomach; however, this is quite below the lethal dose for the average radioresistant gastric cancer. From eight to ten threshold erythema doses (T. E. D.) are necessary to sterilize most carcinomas of the breast and oral cavity, which are on the average less radioresistant than cancers of the stomach.

Holfelder's plan of using a compression diaphragm to exclude the organs overlying the tumor by pressure and replacing with air as much as possible the distance between the target and the tumor has been given a brief trial. In principle, this procedure brings the skin in closer proximity to the tumor and accounts for a relatively greater depth dose to the tumor. The increased dose thus administered is only a small



Fig. 12.—*A*, a roentgenogram of the stomach, showing a defect in the greater curvature of the fundus caused by a bulky papillary adenocarcinoma which could be palpated easily beneath the left costal margin. Metastasis had occurred to the left supraclavicular lymph nodes (signal node of Troisier). *B*, a roentgenogram of the same stomach fourteen months after external irradiation by a radium element pack. The patient gained 40 pounds in weight.

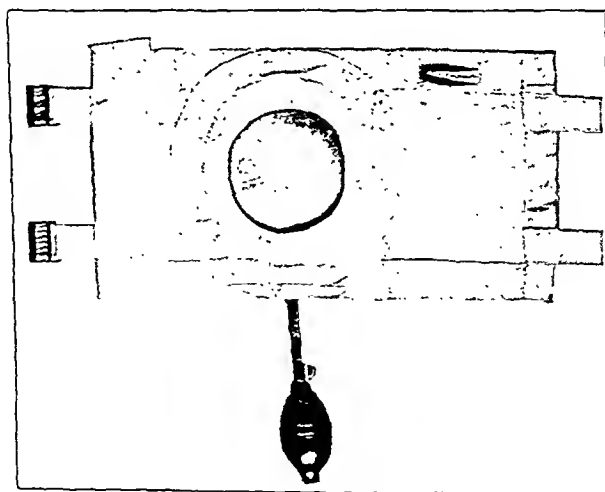


Fig. 13.—The compression belt for roentgenography or radiation therapy. The belt is snugly adjusted with the deflated rubber bag over the abdominal region of the tumor. Inflation brings the skin in closer proximity to the tumor.



fraction of one skin erythema dose and scarcely worth the effort (figs. 13 and 14). The same effect may be obtained by the use of pressure cones.

#### IRRADIATION OF THE BARIUM-FILLED STOMACH

Scholz<sup>31</sup> (1932) thought that the secondary rays in the region of the tumor might be intensified by irradiating the stomach when filled with barium, which not only would protect the adrenal glands by actual filtration but also would make possible sufficient irradiation with a low voltage roentgen ray source. The case reported was one of an inoperable carcinoma (according to the surgeon) which had been explored

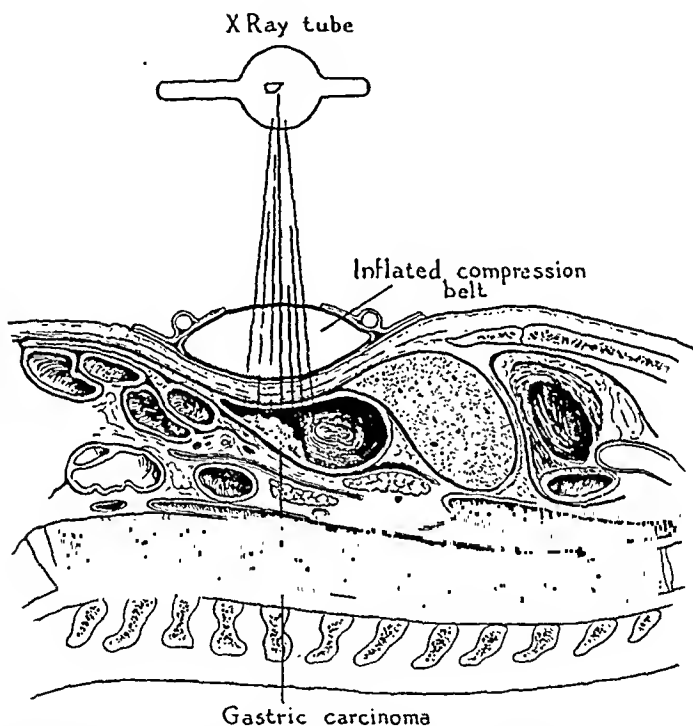


Fig. 14.—Sagittal section through the plane of a gastric cancer. An inflated compression belt is seen applied over the abdominal region of the cancer, bringing the surface of the skin nearer to the tumor. This procedure permits the delivery of a greater depth dosage of radiation to the carcinoma with equivalent erythema doses on the skin.

surgically and for which a gastro-enterostomy had been performed. The patient was well seven years after roentgen irradiation, having a normal stomach on roentgen examination. There was no biopsy of the tumor.

It seems to us that there is little rational basis for irradiation of the barium-filled stomach. The secondary rays produced by the contact of roentgen rays and barium are not deeply penetrating and therefore

31. Scholz, T.: Application of Roentgen Radiation to the Barium Filled Stomach, *Radiology* **18**:269, 1932.

would affect only the surface of the gastric cancer. This technic might be worth while only if the cancer could be thoroughly impregnated with a heavy metal or its salts. There is some conceivable detriment from the nonspecific action of the more caustic secondary rays on the noncancerous mucosa of the rest of the stomach. The only exception by which this principle might properly be applied is in the treatment of the diffuse superficial carcinomas, which are at first limited to the mucosal and submucosal layers. The difficulty here is that this type of gastric cancer is seldom diagnosed until metastases are evident, at which time this method of therapy would not be feasible. With our present technic of fractionated dosage, requiring daily treatments over three weeks, the patients would ingest a dangerously large amount of barium.

#### PREOPERATIVE IRRADIATION OF GASTRIC CANCER

We have not employed preoperative irradiation as a routine for cancers in the distal half of the stomach which we deem operable. There are several reasons for this decision. First, if the lesions are obstructive an operation is immediately necessary. Second, the radiation sickness and the disability for six weeks following intensive irradiation will be too great a handicap for subsequent surgical treatment. Third, it is necessary to wait until the cutaneous reaction to irradiation has subsided before proceeding with the operation. Fourth, preoperative external irradiation is of questionable value in the operable group because as a rule cancer in the distal half of the stomach does not fall in the radiosensitive variety, although lymphosarcoma occasionally occurs in this location. Whenever external irradiation precedes laparotomy, the dose must necessarily be moderate, else great difficulty is encountered in the healing of the wound. Severe radionecrosis of the abdominal wound has occurred three times in our experience, when we had occasion to perform two gastrostomies and one gastro-enterostomy, respectively, for inoperable gastric cancer which had been treated by prolonged roentgen irradiation in fractionated doses.

#### INTERVAL IRRADIATION WITH TWO STAGE RESECTION OF CARCINOMA OF THE STOMACH<sup>32</sup>

The majority of operable cancers situated in the distal half of the stomach can be removed safely by a one stage resection. Some operable gastric cancers occur in elderly patients on whom it may be dangerous to operate because of prolonged pyloric obstruction with its consequent starvation, dehydration and chronic sepsis. When partial pyloric obstruction becomes complete and acute, an emergency arises which

32. Pack, G. T.: Indications for Two-Stage Resection of Carcinoma of Stomach, *S. Clin. North America* 13:517, 1933.

needs prompt surgical intervention. It seems best under such circumstances to relieve the immediate danger of continued pyloric obstruction by quickly performing a gastro-enterostomy, reserving the partial gastrectomy for cancer for a later date, when the water balance of the body is normal, the mineral content of the blood and tissues is restored, the glycogen reserve of the liver and muscles is reestablished and the organism is functioning more normally. The time elapsing between the two operations insures the establishment of good function in the gastro-enterostomy stoma and in the reestablishment of the gastrointestinal gradient. We have given roentgen treatments in the interval between the performance of gastro-enterostomy and resection, although we do not approve of this as a routine measure. If cautiously given it conceivably may retard the growth and dissemination of the cancer, but it is not curative. We mention this procedure because in one instance we found it possible to do a gastric resection twelve weeks after gastro-enterostomy had been done for a cancer of borderline operability, the patient in the meantime receiving an anterior and a posterior cycle of roentgen treatments.

#### CARCINOMA OF THE CARDIA AND FUNDUS

It has been our experience that the most radiosensitive gastric cancers are located in the cardia and the fundus. Such a cancer is usually inoperable because of its location, regardless of the extent of the growth; therefore, there has been little conflict in our decision to employ radium and roentgen rays in lieu of surgical intervention. The percentage of malignant tumors occurring in the cardia is reported in most statistics to be from 8 to 10, but at the Memorial Hospital 20 per cent of the gastric cancers have this regional localization, chiefly because it is an institute for cancer and receives many patients whose condition is deemed inoperable in general hospitals. Tumors in the cardia are more radiosensitive on the average than tumors situated in the distal half of the stomach; the fundal carcinomas constitute the most radiosensitive group of all, but are so relatively few that they do not alter perceptibly the average figures for radiosensitivity of gastric cancer. These cancers metastasize later and less widely than those of other locations in the stomach. The fundal carcinomas are bulky, papillary and vascular, which accounts for their satisfactory response to irradiation. The dangers of complications following irradiation of the cardia are less than in other parts of the stomach. This is particularly true with regard to interstitial irradiation, since the cardia is not in as close proximity to other important organs as is the pylorus and hence tolerates a relatively large dose of radium.

*Use of Gastrostomy in Interstitial Irradiation.*—A Janeway gastrostomy is often done preliminary to interstitial irradiation of cancer of the cardia. This operation constructs a hinged flap of the anterior gastric wall with the base at the greater curvature. The edges of the flap are then sutured to form a goose-neck, which is lined throughout by mucosa. The stoma of the goose-neck is sutured to a small incision in the skin under the left costal margin. This mucosa-lined tube leading into the gastric cavity insures the permanence of the gastrostomy. It serves the valuable purposes of relieving obstruction at the cardia, permitting the intake of sufficient liquid to prevent dehydration and enabling the physician to give the patient a diet of high caloric value which he cannot otherwise take through a persistently stenotic cardia. Moreover, it short-circuits the passage of food into the gastro-intestinal tract and relieves irritation of the cardia from food passing over it as well as from stagnation of food and liquids in the terminal portion of the esophagus. An even more important advantage of such a gastrostomy is the fact that it offers an opening through which direct visualization of the cardia is possible so that gold radon seeds may be implanted into the cancer.

This procedure is performed in the following manner: The gastrostomy stoma is gently enlarged with graduated French Hegar cervical dilators in order to permit the passage of an endoscopic instrument. A child's esophagoscope, cystoscope or bronchoscope can be passed through this stoma into the lumen of the stomach (fig. 15). The patient should not eat any food on the day this treatment is to be given, and it is well to lavage the stomach the night and the morning before this examination is carried out. Any residue of gastric juice found in the stomach is aspirated. After inflation of the stomach with air by means of a bulb attachment, the endoscope is introduced and passed to the cardia, making visualization of the cancer possible. The instrument successfully dilates the cardia and fundus of the stomach, thereby permitting the surgeon to implant gold radon seeds into the carcinoma through especially long hollow trocar needles. Extreme care must be taken not to perforate the stomach and to place the gold radon seeds at the proper distances from each other. The entire dose of radium is seldom given at one time because of the difficulty in exposing the entire tumor. Usually, two, three or four treatments are given in succeeding weeks. In addition to facilitating direct examination this exposure permits repeated removal of material for biopsy, thus enabling the operator to determine the degree of response of the tumor to interstitial radium therapy.

*Surgical Exposure of the Cardia.*—Interstitial irradiation of carcinoma of the cardia may be accomplished either from the mucosal side

through an esophagoscope introduced through a gastrostomy stoma or by direct implantation of gold radon seeds through the seromuscular coat. The latter method is feasible only with proper exposure of the cardia. We have used a modification of the Baudet and Navarro technic for exposing the cardia and fundus by the temporary resection of the left costochondral arch. An incision similar to the one designed by Marwedel is made, extending from the left sternal border in the region of the sixth left costal cartilage and carried downward until it runs parallel to and 1.5 cm. below the costal arch. The incision must be below the costal arch in order to leave sufficient musculature above for suture and closure, and it extends laterally as far as the anterior axillary line. The incision is made through the skin, fascia and muscles down to the plane of the costal cartilages and intercostal muscles. The last

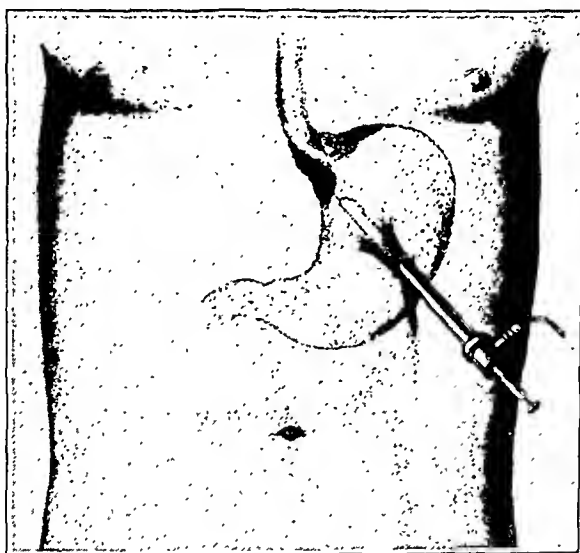


Fig. 15.—Interstitial irradiation of carcinoma of the cardia by the insertion of gold radon seeds through a Janeway gastrostomy. The implantation is done under direct visualization by using a bronchoscope, a cystoscope or a child's esophagoscope.

two ribs of the costochondral arch are severed at a distance of  $1\frac{1}{2}$  inches (3.8 cm.) from the border of the sternum. The last two or three ribs are severed laterally in the anterior axillary line (fig. 16). The line of incision through the ribs should be beveled to permit elevation of this flap. Elevation of this flap upward readily exposes the fundus, cardia, abdominal segment of the esophagus and left lobe of the liver.

The tumor is measured by calipers and the measurements recorded. A satisfactory caliper is the Williams outlet pelvimeter used in obstetrics. The dose of interstitial irradiation is computed so as to supplement the dose delivered from external sources. Gold radon seeds are then care-

fully introduced throughout the substance of the tumor. The trocar needles carrying the gold radon seeds are inserted at an acute angle to the gastric wall so that they penetrate the seromuscular coat obliquely; after traversing this coat for some distance the point of the needle dips inward into the substance of the tumor, where the gold seeds are dis-

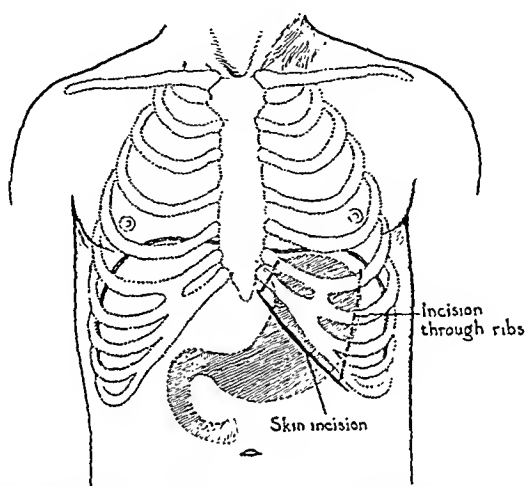


Fig. 16.—Diagram of Marwedel's incision below the costal margin and the Baudet and Navarro technic of elevation of the rib flap to expose the cardia.

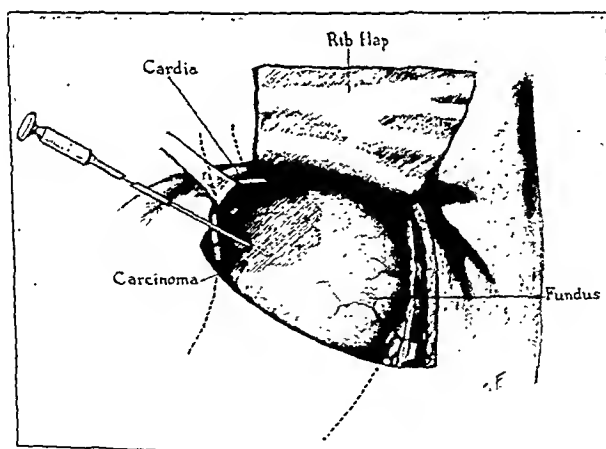


Fig. 17.—A drawing to show retraction of the superficial tissues upward, with elevation of the costochondral flap to expose the cardia. Interstitial irradiation of a carcinoma of the stomach is carried out by oblique insertion of gold radon seeds into the tumor.

lodged and remain. The passage of the needle along an oblique route through the gastric wall insures against the dangers of leakage and perforation (fig. 17).

The costochondral flap is replaced and sutured in position, although one may completely excise it with no deleterious results. If the flap is to be restored, sutures of kangaroo tendon are used at the junction of the cartilages and the ribs. The muscles which were severed transversely along the costal margin are united with mattress sutures. The fascia and skin are closed with interrupted sutures (fig. 18). This wound is subjected to unusually great stress and strain because of respiratory movements, and infection with suppuration is of more frequent occurrence than after the usual abdominal incision.



Fig. 18.—A recent incision for the Baudet and Navarro exposure of the cardia for the implantation of radium. At the same time a Janeway gastrostomy was done, the stoma of which is visible in the upper angle of the separate small wound.

#### IRRADIATION AFTER GASTRO-ENTEROSTOMY WITH EXCLUSION OF INOPERABLE CANCER OF THE PYLORUS AND ANTRUM<sup>33</sup>

Surgeons have found it expedient for radium therapy of carcinoma of the rectum occasionally to do a preliminary colostomy in order to short-circuit the contents. The advantages of this procedure are several; it keeps the rectal carcinoma clean, thus diminishing the degree of infection and the danger of complications, and at the same time affords relief from obstruction. The same principles may be applied

33. Pack, G. T., and Scharnagel, I. M.: Gastro-Enterostomy with Exclusion of Inoperable Cancer of the Pylorus and Antrum, *J. A. M. A.* **102**:1838 (June 2) 1934.

in the irradiation of cancer of the distal half of the stomach. If the tumors in this location are inoperable because of their fixation or metastasis to lymph nodes, etc., the procedure is to perform a preliminary gastro-jejunostomy, especially if obstruction is present and the roentgenograms show retention of the barium meal at the end of six hours. However, a simple gastro-enterostomy is usually not sufficient, because if food continues to come in contact with the pyloric or antral carcinoma the growth will be infected and irritated, thus producing bleeding, toxemia and cachexia. There is also danger of perforation after the interstitial use of radium. We have diminished these dangers by



Fig. 19.—*A*, a roentgenogram of the stomach showing a defect caused by a carcinoma of the cardia. *B*, a roentgenogram of the same stomach made ten weeks after treatment by external and interstitial irradiation.

excluding the carcinomatous portion of the stomach from the proximal normal part.

This operation is performed as follows: In the gastrohepatic and gastrocolic ligaments are made openings that are only large enough to permit the introduction of two soft blades or the de Petz clamp. These blades are clamped proximal to the tumor, and the stomach is severed. The proximal and distal ends are closed by inverted continuous sutures. No attempt at resection is made; the procedure merely closes off the normal proximal part of the stomach from the distal carcinomatous portion. Then a simple posterior or, if necessary, anterior gastrojejunostomy is performed, the normal proximal segment being used. When the irritation subsides in the region of the tumor, the infection rapidly diminishes, bleeding lessens, the patient's appetite improves and he no longer has eructation of gas and foul liquids.



Furthermore, the danger of later occlusion of the gastro-enterostomy stoma by the cancer, if it was extensive when first seen, is prevented.

Two or more weeks after such a palliative operation has been successfully performed, a second small intermuscular incision is made directly over the tumor, usually with local anesthesia. Gold radon seeds in measured tissue doses are implanted in the isolated carcinoma through this exposure. The interstitial irradiation is supplemented by external irradiation, either the radium element pack or high voltage roentgen rays being used. We have not anchored the free carcinomatous segment to the anterior abdominal wall, although this has been suggested.

#### POSTOPERATIVE PROPHYLACTIC RADIATION THERAPY OF GASTRIC CANCER

Irradiation may be instituted within two weeks after an operation without danger of impairing the healing of the wound. We have not, however, employed postoperative radiation therapy as a routine procedure in cases of gastric cancer. In this setting, the decision as to the use of radium or roentgen treatment rests on a histologic analysis of the tumor. If it is of an anaplastic or diffuse radiosensitive variety, it is well to follow the gastric resection by a well planned cycle of high voltage roentgen treatments or by application of a radium element pack externally at a distance; under these circumstances we use a large field of irradiation. For the ordinary cancers of the stomach, such as the fibrocarcinomas, the malignant adenomas, the grade 2 adenocarcinomas and the gelatinous adenocarcinomas, postoperative prophylactic irradiation is not considered necessary, nor have we any evidence that it is worth while.

#### COMPLICATIONS

In addition to radiation sickness and occasional severe leukopenia, there are several other possible complications secondary to the irradiation of gastric cancer. The chief dangers of interstitial irradiation of gastric cancer are three: The needles for introducing the gold radon seeds into the stomach may perforate the wall and thus cause leakage of gastric contents and generalized peritonitis. We have not had this complication in any of the cases in which we have used this treatment. Hemorrhage is another danger, although it must be remembered that such accidents occur spontaneously in patients with carcinoma of the stomach who have had no treatment. Hemorrhage has followed external irradiation, particularly in cases of bulky papillary cancers in which necrosis and solution of the tumor occurred so rapidly that the blood vessels had not had time to become obliterated. In only one case did hemorrhage occur shortly after interstitial irradiation. This patient experienced a severe hemorrhage from a cancer of the cardia two days

after the introduction of four gold radon seeds containing a total of only 6 millicuries.

The last serious complication is late necrosis with ulceration and perforation either to the exterior or into some other abdominal viscus. This accident has happened once in our experience.

A 30 year old man was admitted to the Memorial Hospital with the signs and symptoms of a large advanced carcinoma of the cardia and fundus. When the cardia was exposed, the proximal half of the stomach was found to be occupied by a tumor 14 by 16 cm. in diameter, as large as an average-sized grapefruit. This tumor received a total of 55 millicuries of radon in thirty-seven gold radon seeds. The patient made an immediate uneventful recovery except for mild radiation sickness. Symptoms of a gastrocolic fistula developed six weeks after the interstitial irradiation had been given, and the patient died five days later. Post-mortem examination revealed the establishment of a gastrocolic fistula. The colon had become adherent to the fundus, and ulceration of the necrotic tumor had produced an opening between the two organs. Microscopic examination of this enormous tumor showed almost complete destruction, with only a few carcinoma cells of questionable viability embedded in the scarred tumor base.

#### PATHOLOGIC CHANGES PRODUCED BY IRRADIATION IN CARCINOMA OF THE STOMACH

We have had little opportunity to study the pathologic changes induced in gastric cancer by external and interstitial irradiation, our specimens being limited chiefly to those obtained for biopsy (gastroscopic) or to those seen at occasional necropsies. In the latter case, death occurred at such intervals after irradiation that the residual or recurrent cancers had fully recovered from the effects of this treatment.

The varieties of gastric cancer are so numerous and the dosage and methods of treatment by roentgen rays and radium are so varied that we cannot relate the pathologic changes to any specific form of irradiation. The bulky adenocarcinomas are subject to spontaneous degenerative changes, such as infection, infarction and ulceration. Irradiation adds to this destruction, directly by influence on the cancer cell and indirectly by obliterative vascular changes. The rare papillary adenoma malignum is affected apparently by ischemia induced by thrombosis of the vessels in its stroma, whereas the medullary and diffuse cellular carcinomas seem to regress without noticeable alterations in the tumor bed.

External irradiation either by roentgen rays or by a radium element pack may produce some degree of arteritis with thrombosis, swelling of the collagen and hydropic and atrophic degeneration of cells with later lymphocytic infiltration. Interstitial irradiation in caustic doses causes coagulation necrosis accompanied by small intratumoral hemorrhages with later calcification. Foci of necrosis occur around the

embedded gold radon seeds. The adjacent serosa is covered by a plastic fibrinous exudate. Productive fibrosis, in some cases entombing inactive tumor cells, may be the end-result of proper treatment; necrosis, sloughing, hemorrhage or perforation, on the other hand, may follow too ambitious interstitial irradiation.

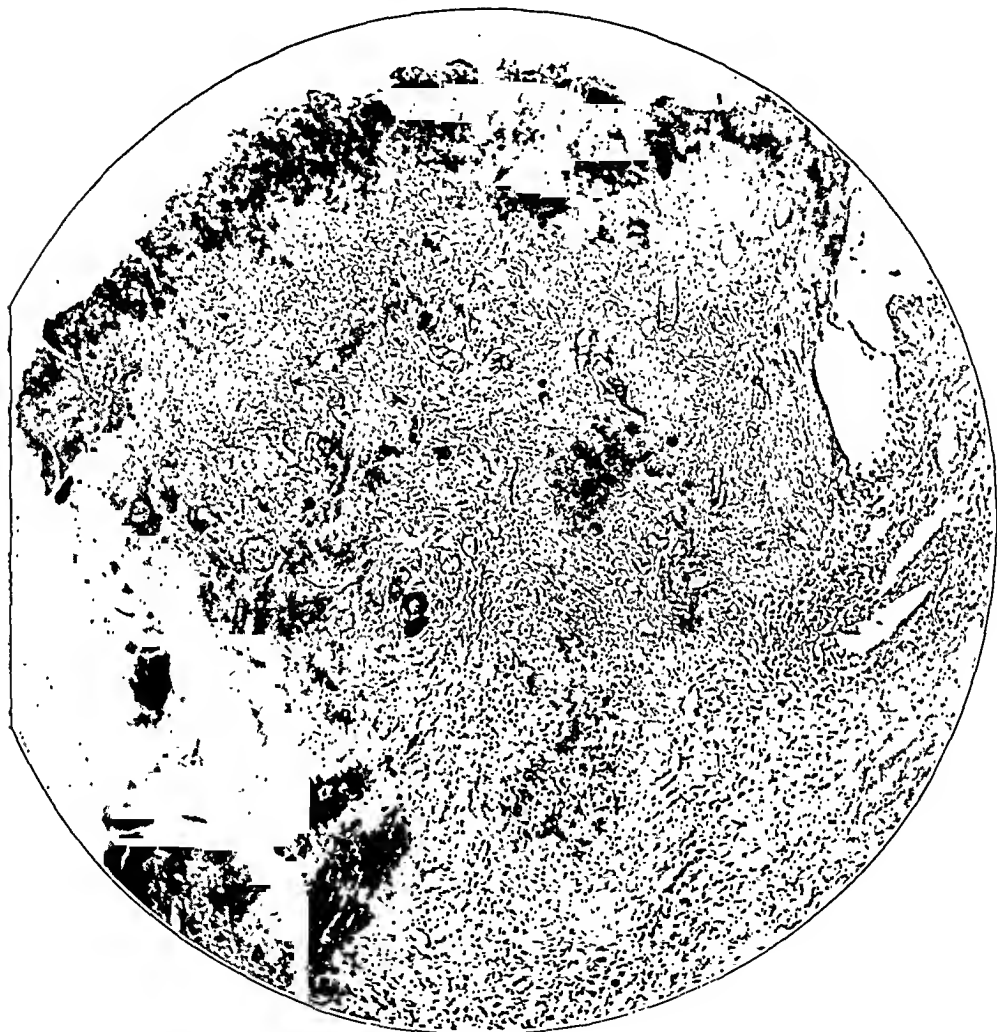


Fig. 20.—Photomicrograph of a section of a bulky adenocarcinoma of the stomach treated by interstitial radium therapy. There are coagulation necrosis and calcification of the tumor, with fibrosis of the bed of the tumor.

#### END-RESULTS

Approximately sixty inoperable gastric cancers have been treated. The majority were situated in the proximal half of the stomach. With the exception of one case, these experiments have been conducted during the last three years. One patient with gastric lymphosarcoma is living and well six years after radiation treatment. Another patient is in good health three years following irradiation of a carcinoma of the

stomach, and two others are without evidence of gastric cancer after an interval of two years. Palliative results are difficult to evaluate, but at least six patients have benefited greatly by these treatments only to succumb later to recurrent activity of residual cancer or to distant metastases. One middle-aged woman with a bulky carcinoma on the greater curvature of the fundus lived comfortably for twenty months and gained 45 pounds (20.4 Kg.) in weight; then generalized carcinomatosis developed, which caused her death three months later. A 40 year old man with a carcinoma occluding the cardiac orifice was able to engage in manual labor for one and one-half years following radiation therapy; he subsequently died of repeated gastric hemorrhages.

It seems self-evident from these results that radiation therapy, however administered, offers little hope for cure to the patient with gastric cancer. The justification for a trial of irradiation is the hope that the cancer may fall into the infrequent group of radiosensitive tumors, which must constitute less than 10 per cent of all gastric cancers. The occasional palliation is more frequent than the apparent cures, and it is this palliative result which has from time to time stimulated us to persist in the face of otherwise discouraging results and almost insurmountable technical difficulties. It would be unfair to compare these results with those of surgical treatment because only inoperable cancers are selected for radiation therapy. Whatever advantages or benefits have occurred to any of these sixty treated patients are over and above what could have been given them by surgical measures, by the very definition of the term inoperable. Radiation therapy is not proposed as a substitute for surgical treatment of operable gastric cancer.

#### SUMMARY

1. Gastric cancer was the first type of tumor ever treated by roentgen rays.

2. The disadvantages of irradiation of gastric cancer are: (a) the daily utilization of the stomach in feeding, (b) the inaccessibility of the stomach and the consequent low tissue dose delivered by external irradiation, (c) the danger of laparotomy for interstitial irradiation, (d) the degree of radiation sickness following treatment, (e) the extent of the cancer, as only inoperable gastric cancers are treated by irradiation, and (f) the frequent obstruction of the cardia and pylorus by these cancers.

3. Less than 10 per cent of gastric cancers exhibit any considerable degree of radiosensitivity. These rare radiosensitive cancers are usually situated in the cardia and fundus or on the greater curvature of the stomach.

4. There is a certain anaplastic small cell gastric cancer which bears a close morphologic resemblance to lymphosarcoma and is sensitive to radiation.

5. Gastric cancers have been treated by roentgen rays, radium element pack, interstitially implanted radium and combinations of these agents. The tissue dose delivered to the tumor in each case has been determined and expressed as skin erythema units. External irradiation is given through several ports to cross-fire at the stomach; the Coutard technic of fractionated dosage is the procedure of choice. The radium element pack is the most effective agent for external irradiation of gastric cancer.

6. We believe that there is little rational basis for irradiation of the barium-filled stomach. Several reasons are given that preoperative irradiation of resectable gastric cancer is not advisable. Interval irradiation with two stage resection of carcinoma of the stomach has been employed for cancers of borderline operability situated in the distal segment.

7. Carcinomas of the cardia have been treated by the implantation of gold radon seeds in addition to external irradiation. The radon seeds are implanted through an endoscope inserted in an opening made by gastrostomy as well as through the seromuscular coat, after exposure of the cardia by resection or elevation of a left costochondral rib flap.

8. Inoperable pyloric and antral carcinomas are treated whenever possible by irradiation after gastro-enterostomy with exclusion of the cancerous distal segment of the stomach.

9. Postoperative prophylactic radiation therapy is reserved only for those operable gastric carcinomas which on histologic analysis are shown to be among the rare anaplastic radiosensitive tumors.

10. The possible complications of irradiation of gastric cancer are (a) radiation sickness, (b) peritonitis, (c) gastric hemorrhage and (d) necrosis and the formation of fistulas with adjacent viscera.

11. Radiation therapy is a palliative rather than a curative measure for gastric cancer.

#### REPORT OF CASES

CASE 1.—A. E., a married white woman aged 46, applied to the Memorial Hospital for treatment on Jan. 2, 1929. She first complained of dysphagia and epigastric pain in January 1928. These symptoms increased in severity until May 1928, at which time roentgenograms of the gastro-intestinal tract showed a bulky tumor involving the cardia and the pars media. The diagnosis was confirmed at operation; a biopsy specimen was obtained from an inoperable tumor the size of a grapefruit. The tumor was composed of small hyperchromatic cells growing diffusely in a scant stroma with no tendency to form alveoli. Dr. Ewing and Dr. Stewart have been undecided whether to classify this tumor histologically as an anaplastic carcinoma or a lymphosarcoma but have leaned toward the latter diagnosis.

Treatment was entirely by irradiation, high voltage x-rays being employed in San Francisco late in 1928 and treatment by the 4 Gm. radium element pack at the Memorial Hospital in January 1929. With the radium pack, 48,000 milligram hours were given at a distance of 15 cm. anteriorly and posteriorly to cross-fire at the stomach. The tissue dose delivered to the tumor by the roentgen treatments was one and one-fifth skin erythema dose; by the radium element pack, four-fifths of a skin erythema dose.

The patient improved rapidly, regained her appetite and good digestion and gained weight. Repeated roentgenographic examinations have failed to reveal any filling defects or abnormalities in the stomach. The last verbal report in June 1935 from the patient, who is now residing in California, was that she was in excellent health, with no symptoms referable to her stomach.



Fig. 21 (case 1).—*A*, a roentgenogram of the stomach showing a defect caused by an annular anaplastic small cell carcinoma of the antrum. *B*, a roentgenogram of the same stomach made three years after external irradiation by high voltage roentgen rays and a 4 Gm. radium element pack.

This patient has received seven years of life and good health following the successful irradiation of an inoperable primary gastric sarcoma.

CASE 2.—M. P., a Hungarian housewife aged 48, applied to the Memorial Hospital on Nov. 26, 1930, complaining of a tumor in the abdomen, of which she had been aware for three weeks. The gynecological, past and family histories were irrelevant.

The only noteworthy finding on physical examination was an abdominal tumor in the umbilical region, readily visible to inspection. It was well defined at its lower edge, which extended below the umbilicus. It had a smooth contour and firm consistence and moved with respiration. There was persistent absence of free hydrochloric acid after the administration of beta-iminazoly-ethylamine hydro-

chloride. The blood count was normal in spite of apparent anemia. The Wassermann reaction was negative.

Roentgenograms of the stomach made on December 3, after the ingestion of barium revealed evidence of extensive involvement of the prepyloric segment, the appearance indicating carcinomatous infiltration of the gastric wall. There was 30 per cent retention of the barium meal at the end of six hours.

Permission to operate was refused; therefore on December 31, a cycle of high voltage roentgen irradiation was started, being delivered through four portals at intervals of from three to four days with a dose of 762 roentgens to each field. Starting on Feb. 9, 1931, and continuing over a period of six weeks, further external irradiation was administered with the 4 Gm. radium element pack at a skin distance of 15 cm., 75,000 milligram-hours being given anteriorly and the same dose posteriorly. The tissue dose delivered to the tumor by the roentgen treatments was one and seven-tenths skin erythema dose; by the radium element pack, one skin erythema dose, totaling two and seven-tenths skin erythema doses by both agents.

Roentgenographic studies of the stomach in November 1931 showed marked improvement with little evidence of involvement and no retention at the end of six hours. A third series of roentgenograms made in January 1933 showed no evidence of organic disease. Analysis of the gastric contents in April 1933 again showed persistent achlorhydria. The abdominal tumor has not been palpable for two and one-half years. The patient's weight is normal, and she has no symptoms referable to the gastro-intestinal tract. In April 1934 a third gastric analysis was made, revealing 70 degrees of free hydrochloric acid after the administration of beta-iminazoly-ethylamine hydrochloride and the presence of occult blood in the gastric juice. Further roentgenographic studies, made in May 1934, showed a small deformity somewhat similar to that seen on the first films, taken three and one-half years before. The patient will not accept operative intervention.

CASE 3.—S. P., a Jewish man aged 52, was admitted to the clinic for gastric diseases at the Memorial Hospital on Nov. 22, 1932. He was a painter who for a year and one-half had suffered from occasional attacks of nausea and vomiting and later from an aching and boring epigastric pain which was more severe after eating. The vomiting increased in frequency, and he had lost 19 pounds (8.6 Kg.) in weight.

Physical examination showed a poorly developed and undernourished man in poor general condition. His oral hygiene was poor. There was slight tenderness in the epigastric region but no palpable mass. The hemoglobin registered 50 per cent, and the red blood cells numbered 2,500,000 per cubic millimeter. Gastric analysis showed 80 degrees of free acidity in the specimen obtained when the patient was fasting and 92 degrees total acidity. The Wassermann reaction was negative. Roentgen examination of the stomach with a barium meal revealed an irregularity of the greater and lesser curvatures in the distal third of the stomach. There was a large residue of barium in the stomach after six hours. Because of the character of the pain and the high gastric acidity, the presence of a gastric ulcer was considered more likely than carcinoma. Yet the roentgenologists diagnosed the lesion as carcinomatous and pointed out that all ulcers on the greater curvature were invariably cancer. We recently had an opportunity to study a very malignant gastric cancer which was associated with hyperacidity.

The patient was advised to follow a modified Lenhartz diet with alkaline therapy and was warned of the danger of perforation. Thirteen days after the first observation he was admitted to the hospital because of severe epigastric pain. An emergency operation for a ruptured gastric ulcer was done; this revealed a bulky cancer involving the lesser and greater curvatures up to 3 finger-



Fig. 22.—*A*, a roentgenogram of the stomach showing a carcinoma encircling the antrum and pylorus, causing stenosis of a moderate degree. *B*, a roentgenogram of the stomach six hours after a barium meal to show the degree of retention. *C*, a roentgenogram of the same stomach thirty months after intensive irradiation by a radium element pack. *D*, a roentgenogram of the stomach six hours after a barium meal to show the disappearance of the pyloric obstruction.

breadths from the cardia. The peritoneal cavity contained considerable gastric contents. A crevice 5 cm. long extended into the gastric lumen through the base



of the transverse mesocolon. The tissues were too friable to suture; so the great omentum was packed into the wound as a tampon and sutured in place. The abdomen was closed with drainage. A blood transfusion was given. The patient improved gradually after a stormy convalescence. Five weeks after the operative procedure he was able to receive roentgen irradiation to the entire abdomen given at a target skin distance of 150 cm. During two such cycles of therapy the palpable tumor and the marked ascites disappeared, and the patient gained 20 pounds (9.1 Kg.) in weight.

As the mass could be slightly palpated four months later, one cycle of high voltage roentgen radiation was given at a target skin distance of 70 cm., 1,200 roentgens being delivered in divided doses anteriorly and posteriorly. In December 1933 the patient was readmitted to the hospital, and an anterior gastroenterostomy with lateral entero-anastomosis was performed. A biopsy specimen taken at this time from the scarred fibrotic tumor showed gastric cancer in a state of abortive fibrosis. Additional roentgen irradiation followed this procedure, after which the patient again gained weight and his digestion became very good. He is in excellent health now, two years after the initial irradiation.

CASE 4.—C. G., a Mexican man aged 67, began to suffer from postprandial epigastric pain, eructation of gas, anorexia, loss of weight and occasional vomiting in October 1932. Roentgenograms made in January 1933 with a barium meal showed a cascaded outline of the stomach with a deep persistent incisura on the greater curvature and a constant defect in the cardia. There was retention of a large amount of gastric residue after five hours. The diagnosis by three roentgenologists in as many hospitals for cancer was inoperable cancer of the stomach. Very small doses of high voltage roentgen irradiation given in January 1933 were followed by relief from symptoms and gain in weight.

In May 1933 no masses or tenderness were found by abdominal palpation, and the gastric contents one hour after the injection of beta-iminazoly-ethylamine hydrochloride contained 56 degrees of free acidity expressed in terms of tenth-normal sodium hydroxide. All specimens of gastric juice still contained blood. Roentgen studies of the stomach at this time showed an hour-glass deformity with no retention after six hours. The Wassermann reaction was negative.

Further external irradiation was given through anterior, posterior and left lateral portals with the 4 Gm. radium pack at a skin distance of 15 cm. Eighty gram hours was given to each portal. Roentgenograms made following the reaction to this therapy showed decided improvement. The same treatment was repeated in December 1933. Some cicatricial contraction following this cycle is probably due to scar tissue. The patient has gained 25 pounds (11.3 Kg.) in weight and has no symptoms almost two years after the first irradiation.

## FRACTURES OF THE BASE OF THE RADIUS IN ADULTS

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This study is based on a series of 155 cases of fracture of the base of the radius by indirect violence in 140 adults, observed in hospital and private practice and all personally examined by me.

As 10 per cent of all fractures<sup>1</sup> occur at the base of the radius and as the literature on the subject exhibits such diversity of opinion concerning etiology, pathologic process, treatment and end-results, this study was undertaken in 1926. It has been continued since then and includes cases of fracture occurring between the years 1913 and 1932.

The average length of time that elapsed between the fracture and the follow-up examination was sixteen months and the longest time nineteen years, while no case has been included in which the fracture had occurred less than three months prior to the follow-up examination.

Throughout this study an attempt has been made to correlate the anatomic with the cosmetic and functional results. To this end, the follow-up examination consisted of the taking of an adequate history, a thorough physical examination and roentgenograms of both wrists.

In the history, special note was made of subjective complaints, the length of time and the type of disability and the ability of the patient to resume his previous occupation.

The injured wrist was examined and compared with the sound one for bone deformities, local tenderness and limitation of motion. An angiometer was employed in the measurement of flexion and extension, while abduction, adduction, pronation and supination were compared with the normal motions in the opposite wrist and the results were recorded merely as an increase or decrease on the affected side. The circumference of each wrist and the radiocarpal articulation and the actual gripping power of each hand were measured and recorded. Attention was also paid to the range of motion of the fingers, the presence of injuries to the nerves and other soft tissue and the extent of arthritis, when present.

After the physical examination, roentgenograms were made of both wrists on the same plate. Both anteroposterior and lateral views were

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Read before the Section of Surgery of the New York Academy of Medicine, Dec. 1, 1932.

1. Adams, E.: The Symptoms and Treatment of Colles' Fracture, *Internat. J. Surg.* **24**:140, 1911.

made in each case. These were compared carefully with the films made at the time of reduction whenever the latter were available.

In the roentgenograms made at the follow-up examination particular attention was paid to the following points: (1) type of fracture, (2) comminution, (3) shortening of the radius, (4) widening of the wrist joint and the base of the radius, (5) spreading of the inferior radio-ulnar articulation, (6) tilting of the distal radial fragment and (7) fracture of the styloid process of the ulna and nonunion between it and the ulnar shaft.

#### MEASUREMENT OF BONE DEFORMITY

Simple methods were devised for actual measurement on the roentgenograms of the major bone deformities noted at the follow-up examination.

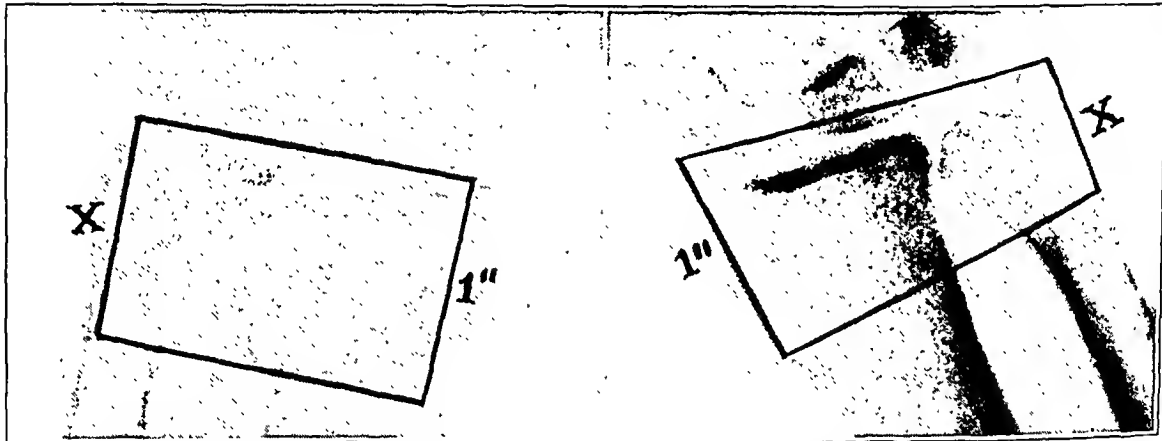


Fig. 1.—Diagram of the method of measuring the shortening of a radius.

*Shortening of the Radius.*—To measure shortening of the radius, a quadrilateral figure is constructed on the anteroposterior view of the roentgenogram of the sound wrist and a similar figure is constructed on the roentgenogram of the fractured wrist. A straight line is drawn from the tip of the styloid process of the radius to that of the ulna. A second straight line is drawn from the tip of the styloid process of the radius to a point 1 inch (2.5 cm.) proximal on its lateral border. From the proximal end of this line a third line is projected across both the radius and the ulna perpendicular to the long axis of the radius. The quadrilateral is completed by a fourth line, X, from the tip of the ulnar styloid process to the point where the third line crosses the medial border of the ulna. The difference between the X lines on the two quadrilaterals indicates the shortening of the fractured radius.

*Widening of the Wrist Joint.*—Using the anteroposterior view of each wrist, a line is drawn from the lateral border of the radius to the medial border of the ulna perpendicular to the long axis of the radius and at the level of the base of the ulnar styloid process. A comparison of these lines gives the amount of widening of the injured wrist joint. Similarly, widening of the base of the radius itself is determined.

*Tilting of the Distal Radial Fragment.*—Using the lateral view of each wrist, one straight line is drawn across the plane of the carpal articular surface of the radius, and another line is drawn parallel to the long axis of the radius. The difference between the angles, X, formed by the intersection of these lines on the two figures indicates the degree of tilting of the distal radial fragment in the fractured wrist. As the plane of the articular surface of the radius is normally tilted slightly forward, when this plane in the fractured wrist is level it may arbitrarily be considered as first degree posterior tilting; if just beyond a level plane, second degree, and if markedly tilted, third degree. Anterior tilting, when present, can be measured by the construction of the same kind of figure.

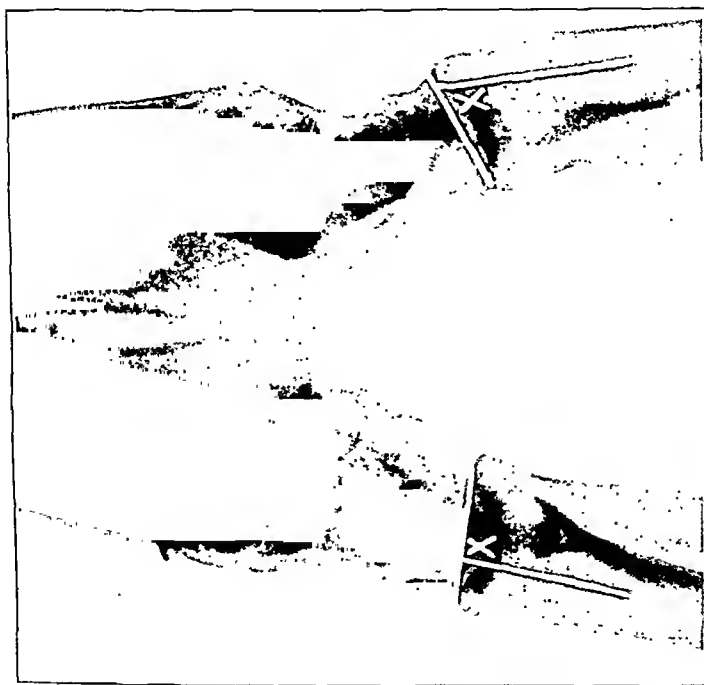


Fig. 2.—Diagram showing the angle of backward tilting at the base of the radius compared with the normal angle on the slide.

*Anatomy.*—For a better understanding of the etiology of these fractures it will be worth while to consider a few salient points in the anatomic structure of the wrist joint.<sup>2</sup> The carpal articulating surface of the radius is shallow, tilted forward and impressed with two fairly well defined grooves for contact with the scaphoid (navicular) and the semilunar (lunate) bones. On its medial aspect the base of the radius articulates with the ulna both directly and through the interarticular fibrocartilage. The cortex of the radial shaft, while fairly heavy at the

2. Morris, H.: Human Anatomy, ed. 5, Philadelphia, P. Blakiston's Son & Co., 1914.

base, becomes appreciably thinner at the site of the old epiphyseal line. Finally, the ligamentous attachments around the wrist joint are analogous to those about the ankle. There are three pairs of ligaments: (1) the radial and ulnar collateral ligaments, extending from the styloid processes to the carpal bones; (2) the anterior and posterior radio-carpal ligaments, (3) and the anterior and posterior radio-ulnar ligaments.

#### ETIOLOGY AND CLASSIFICATION

It seems advisable to consider the etiology of the aforementioned fractures in order more intelligently to classify and interpret the end-results noted.

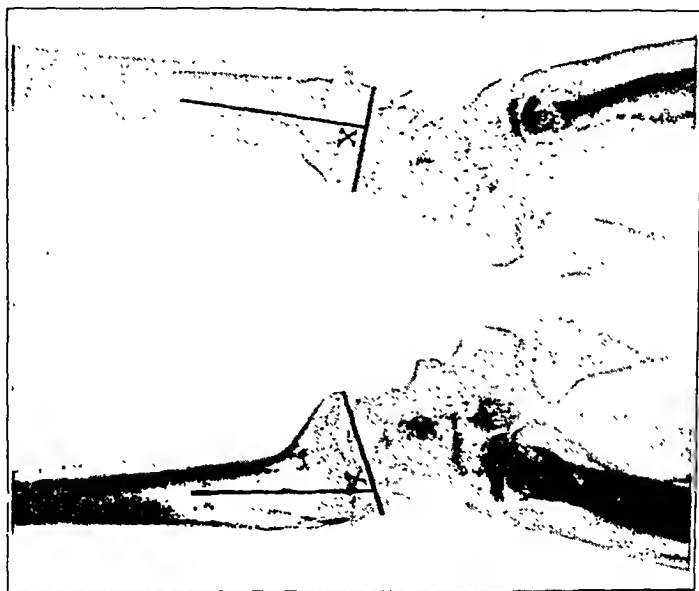


Fig. 3.—Diagram showing anterior tilting of the base of the radius in cases of overcorrection.

Fracture by indirect violence about a joint such as the wrist or ankle would necessarily be one of a few constant types, depending on the direction of the lines of force responsible for the fracture. The two factors principally involved may be called pull and push. Pull is the primary force and is exerted by the ligaments, while push is secondary and involves the pressure of bone against bone.

For instance, in a simple transverse fracture of the base of the radius the ligamentous pull causes the bone to break transversely and at a rather constant level. This has been described as *arrachement*. If the fracturing force is continued beyond this point to the pull, there is superadded a push, or pressure, against the distal radial fragment by the scaphoid and/or semilunar bone from below and by the proximal

radial fragment from above. The resultant fragmentation and extent of injury to the distal radial fragment will depend on the amount and direction of the push.

As man walks only on his lower extremities, nature provides a rear process or heel for the foot, so that fracture by indirect violence occurs in a lateral rather than in an anteroposterior plane. But the hand has no heel process, and therefore there is a tendency for fracture by indirect violence to occur in an anteroposterior plane and less frequently in a lateral plane.

On the theory, then, that fractures about the base of the radius by indirect violence in adults are dependent on the amount and direction of the force applied, there was evolved the following simple classification of such fractures, into some subdivision of which each of the 155 cases of this series seems naturally to fall:

I. Simple transverse fractures (arrachement<sup>3</sup>)

II. Comminuted transverse fractures

- A. Extension or flexion force (scaphoid and semilunar),<sup>4</sup> Y or T types
- B. Abduction force (scaphoid)<sup>5</sup>
- C. Adduction force (semilunar)<sup>5</sup>
- D. Avulsion force (intermediary fragment,<sup>6</sup> styloid fracture<sup>4</sup>)
- E. Lateral splitting force<sup>7</sup> due to the thrust of the proximal radial fragment into the distal radial fragment<sup>8</sup>

*Simple Transverse Fractures.*—It is well known that sufficient force exerted on the lower end of the radius through the ligaments about the wrist joint, as from a fall on the hyperextended hand, will result in a transverse fracture of the radius at a distance of from  $\frac{1}{2}$  to  $\frac{3}{4}$  inch (1.2 to 1.9 cm.) proximal to its base. Jones<sup>9</sup> stated that as the dorsal lip of the carpal articular surface of the radius extends to a more distal level than the volar surface, it is bound to receive the full propulsive force of the carpus. It has been demonstrated by Pilcher<sup>10</sup>

3. Cotton, F. J.: Dislocations and Joint Fractures, ed. 2, Philadelphia, W. B. Saunders Co., 1924.

4. Cotton, F. J.: The Pathology of Fracture of the Lower Extremity of the Radius, Ann. Surg. **32**:194 and 388, 1900.

5. Gallois, E.: Fracture de l'extrémité inférieure du radius: Étude radiographique, physiologique et expérimentale, Lyon, L. Bourgeon, 1898.

6. Kaufman, C.: Diagnose und Behandlung der subkutanen Radiusfraktur am Handgelenke, Deutsche Ztschr. f. Chir. **45**:531, 1897.

7. Hamilton, F. H.: Practical Treatise on Fractures and Dislocations, ed. 6, Philadelphia, Lea & Febiger, 1880, p. 305.

8. Bennett, E. H.: On the Rarer Forms of Fracture of the Carpal Extremity of the Radius, Tr. Roy. Acad. Med. Ireland **10**:322, 1891-1892.

9. Jones, R.: Analysis of One Hundred and Five Cases of Colles' Fracture, with a Few Remarks on Treatment, Liverpool M.-Chir. J. **5**:430, 1885.

10. Pilcher, L. S.: Fractures of the Lower Extremity or Base of Radius, Philadelphia, J. B. Lippincott Co., 1917.

and Speed<sup>11</sup> that the cross-strain causing the fracture is exerted at the ligamentous insertions just at or below the old epiphyseal line. There is a pulling apart of the anterior surface of the radius along a transverse line, while along a much wider area on the posterior surface there

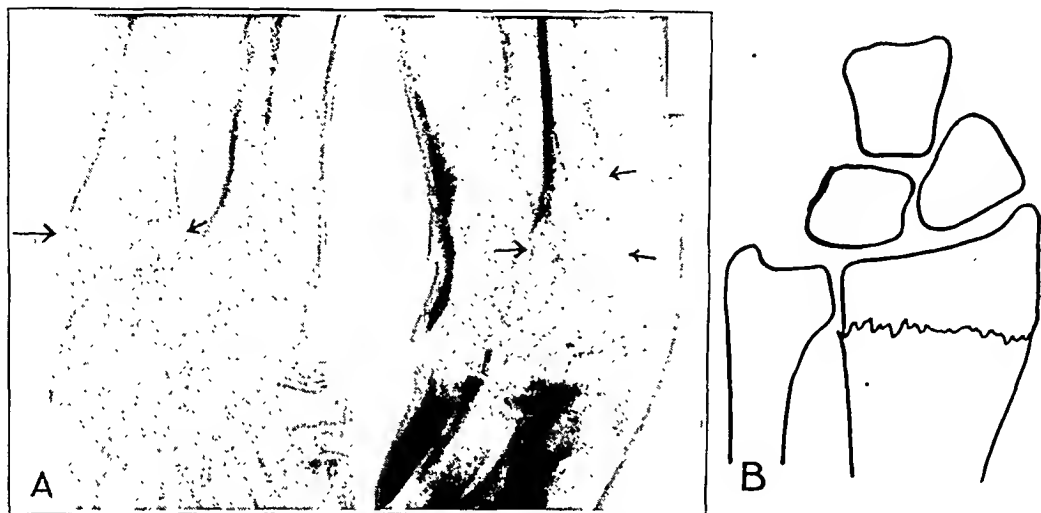


Fig. 4.—Roentgenogram (A) and diagram (B) of a simple fracture (arrachement), showing a simple fracture of the base of the radius, with the zone of bone injury plainly visible in A.

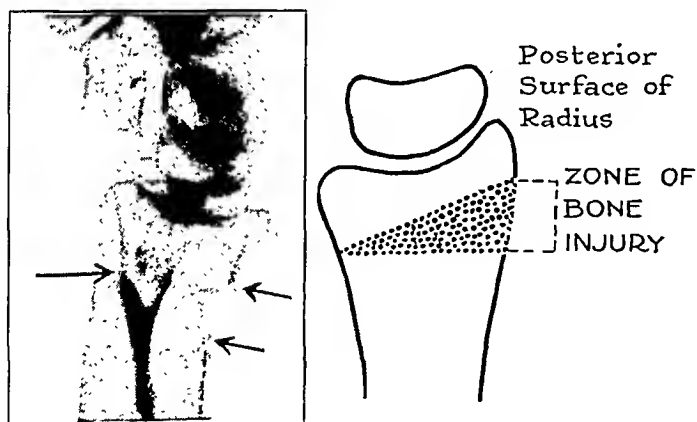


Fig. 5.—Lateral roentgen views before reduction, showing posterior crushing of the radius at the site of fracture and the extent of the zone of bone injury.

are compression and crushing of bone tissue. The result is a triangular area of bone injury, with the base of the triangle toward the dorsum of the radius. This may be termed the zone of bone injury.

11. Speed, K.: *Traumatic Injuries of the Carpus, Including Colles' Fracture*. New York, D. Appleton-Century Company, Inc., 1935.

According to Cotton,<sup>4</sup> shortening of the radius is due to the actual destruction of bone tissue, which is particularly likely to occur posteriorly. Such a zone can be demonstrated in the roentgenogram of practically every one of these fractures. The shape of this triangular zone of bony injury may be altered by the surgeon jamming the fragments into acute flexion, thereby causing more shortening by added injury to the anterior border of the fracture.

The fracturing force carries the hand and the distal fragment of the radius upward and backward. In addition, because the distal fragment of the radius usually remains attached to the ulna by the inferior radio-ulnar ligaments, the hand and this fragment are revolved into supination about the ulna as a pivot. Pilcher<sup>10</sup> spoke of this as supinating rotation. Knott<sup>12</sup> expressed the opinion that the triangular fibrocartilage acts as the radius of an arc through which the distal

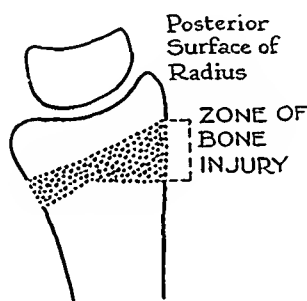


Fig. 6.—Diagram showing alteration of the shape of the zone of bone injury by forceful flexion in reduction.

fragment of the radius rotates, the outer side of the latter describing a greater arc than the inner side.

*Comminuted Transverse Fractures.*—A. Extension or Flexion Force (Scaphoid and Semilunar): The os magnum (capitate) is the key bone of the carpus. Because of its strategic relation to the scaphoid (navicular) and semilunar (lunate) bones, it undoubtedly plays an important rôle in determining the type of comminution frequently observed in the distal fragment of the radius. On this Rotter<sup>13</sup> laid great stress. He has shown, with blocks, how the distal fragment is split into portions corresponding roughly to the articular facets of the scaphoid and semilunar bones by a force transmitted straight upward through the os magnum, thus producing a T or Y fracture.

12. Knott, J. F.: Colles' Fracture, *M. Press & Circ.* 31:69, 89 and 111, 1881.

13. Rotter, H.: Ueber Frakturen des Radius am unteren Ende. *Deutsche Ztschr. f. Chir.* 156:235, 1920.



B. Abduction Force (Scaphoid): With the hand in abduction, the os magnum is brought with greatest force against the scaphoid bone, and scaphoid fragmentation of the radius results.

Eliason<sup>14</sup> stated that the line of fracture depends on the position of the carpus and whether the force is transmitted through the thenar or the hypothenar eminence. Lucas<sup>15</sup> demonstrated these facts on dissected specimens.

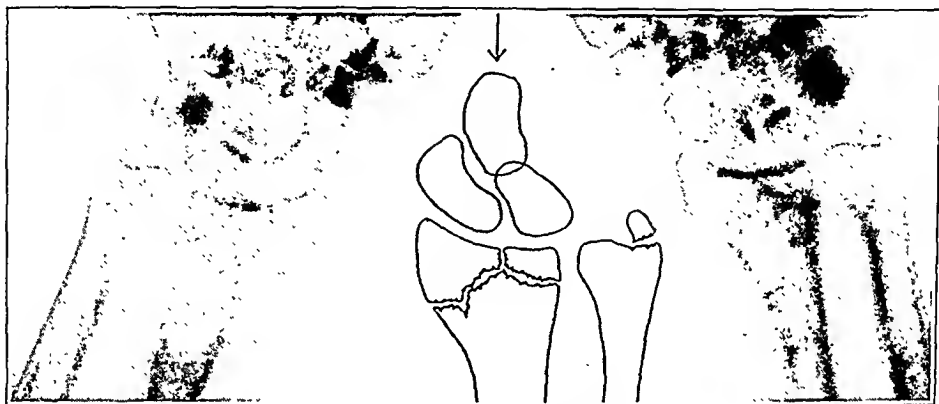


Fig. 7.—Roentgenogram and diagram showing the Y type of fracture (comminuted).

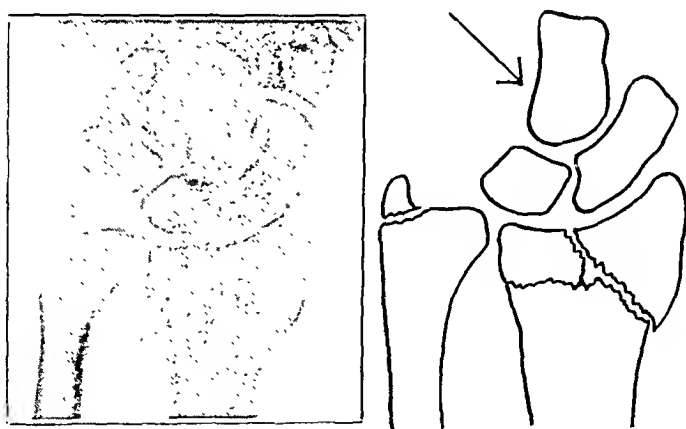


Fig. 8.—Roentgenogram and diagram showing the abduction type of comminution.

C. Adduction Force (Semilunar): Conversely, with the hand in adduction, the semilunar bone often breaks off a distinct fragment of the radius and may even fracture the end of the ulna.

14. Eliason, E. L.: *Fractures of the Humerus, Radius and Ulna*, New York, D. Appleton & Company, 1925.

15. Lucas, R. C.: *On Colles' Fracture*, *Guy's Hosp. Rep.* 42:375, 1883-1884.

D. Avulsion Force: In addition, in a large number of cases in the group of comminuted fractures I noted avulsion of a small intermediate fragment of bone by the inferior radio-ulnar ligament, analogous to the intermediate fragment of Tilleaux in fracture of the ankle. This type of fragmentation was mentioned by Kaufman,<sup>6</sup> Eliason<sup>14</sup> and Cotton,<sup>4</sup> who quoted the observations of Beidenhauser. The tendency of the

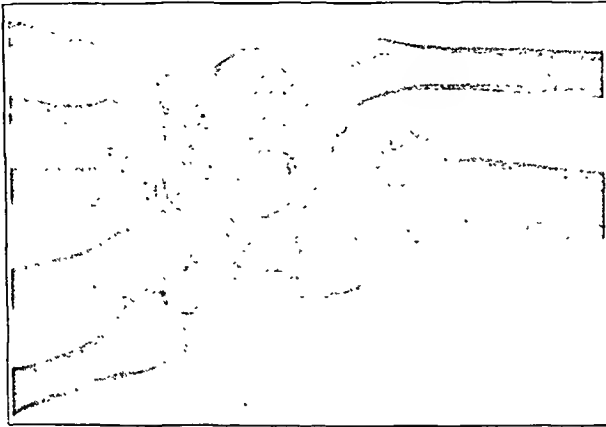


Fig. 9.—Roentgenogram and diagram showing the adduction type of comminution.

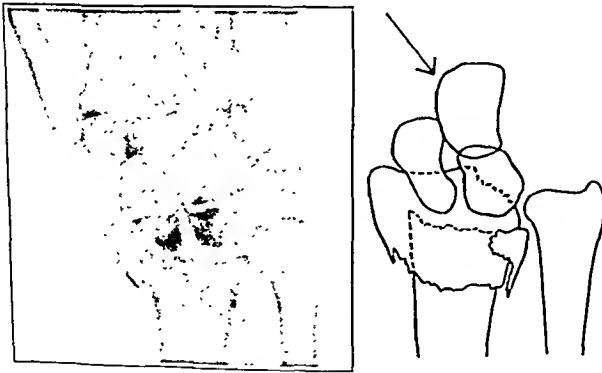


Fig. 10.—Roentgenogram showing tearing off of the intermediate fragment by avulsion force of the inferior radio-ulnar ligaments.

distal fragment of the radius to rotate into supination, already mentioned, doubtless acts as an additional avulsing force, as the fragment seems to be torn from one corner of the base of the radius.

Fracture of the styloid process of the ulna is due to avulsion by the ulnar collateral ligament as the carpal bones are suddenly carried away from it (fig. 8). There is no doubt that the inferior radio-ulnar

ligaments are occasionally torn apart,<sup>7</sup> as shown by permanent widening of that articulation in 26 cases of this series.

E. Lateral splitting of the distal fragment could actually be demonstrated in the lateral view of the roentgenogram in 63 cases. The result of this was usually a widening of the distal fragment in the lateral view.

#### ANALYSIS OF OBSERVATIONS ON CASES

*Incidence According to Age.*—It is well known that age is an important factor in these injuries, as has been reported by Hitzrot and Mur-

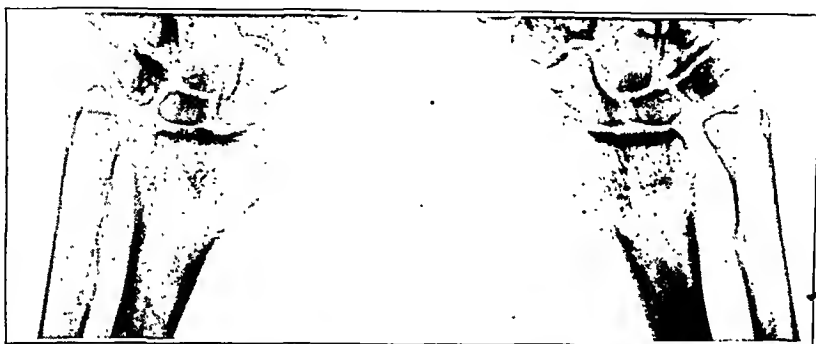


Fig. 11.—Roentgenograms showing widening of the inferior radio-ulnar joint caused by tearing of the ligaments.

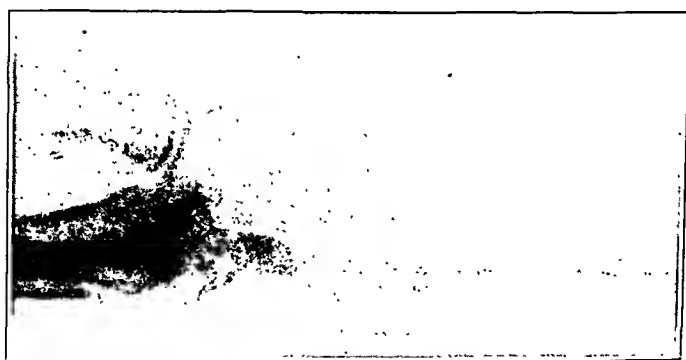


Fig. 12.—Lateral roentgen view showing splitting of the distal fragment.

ray.<sup>16</sup> The youthful adult does not, as a general rule, sustain such extensive damage to the bones from a given trauma, and his convalescence is shorter than that of a person past 35. Also, the best results are obtained in youthful patients.

The average age in this series was 44 years. It will be seen in table 1 that the greatest number of cases occurred in persons between the ages of 40 and 60, and doubtless this is a fair representation of the

16. Hitzrot, J. M., and Murray, J. R.: The Factors That Influence the Prognosis in Fractures at the Base of the Radius, *Am. J. Surg.* 35:17, 1921.

practice of any urban hospital in which there is no selection of emergency cases. It would tend to emphasize the importance of advancing age, with its accompanying impaired eyesight and the loss of sureness of foot, with consequent falls and injuries to bones that are older and more brittle. The rather high percentage in the decade from 20 to 30 probably represents increased activity in dangerous occupations, strenuous sports and the like.

*Type of Fracture.*—On the basis of etiology, the cases may be grouped in accordance with the classification presented elsewhere in this paper (table 2).

TABLE 1.—Incidence According to Age in One Hundred and Forty Adults

Age, Years	Number of Cases	Percentage of Total
20 to 30.....	23	19.5
30 to 40.....	20	14.2
40 to 50.....	34	24.2
50 to 60.....	23	23.5
60 or over.....	25	17.8

TABLE 2.—Type of Fracture in One Hundred and Fifty-Five Cases \*

Classification	Number of Cases	Percentage of Total
1. Simple transverse fracture (no evidence of comminution)...	45	29.0
2. Comminuted fracture		
A. Extension or flexion force (scaphoid and semilunar)	43	27.6
B. Abduction force (scaphoid).....	17	10.9
C. Adduction force (semilunar).....	13	8.3
D. Avulsion force		
Intermediate fragment .....	25	29.7
Styloid fracture .....	101	65.0
E. Lateral splitting force.....	63	40.6
3. Type not determined .....	37	23.7

\* Fifteen of the 140 patients had a bilateral fracture.

The proportion of cases of simple transverse fracture is probably high, because many of the roentgenograms on which this study is based were made promptly after the fracture and reduction instead of two or three weeks later when, as has repeatedly been demonstrated, all lines of fracture stand out more clearly. It even happens that some lines which were not seen on the original films are plainly visible on those taken later, owing to absorption along the lines of fracture. So it is possible that in some of the cases the condition classed in table 2 as simple transverse fracture was in reality comminuted. In most of the cases in the "type not determined" group the fracture was, as a matter of fact, comminuted, but the type of the comminution was not discernible by roentgen study, the healing process having progressed so far as to obscure the original displacement of fragments.

Incidentally, the right wrist was injured in 59 cases, the left in 66 and both in 15. This is a matter of more or less academic interest, except that when both wrists were fractured there was usually a history of increased violence, such as a fall from a considerable height.

*End-Results.*—Of the 140 patients in this series 100 (71 per cent) had returned to, and were employed in, their previous occupation at the time of the follow-up examination; and 14 (10 per cent) were not working. In 26 cases (18 per cent) the fact whether or not the patient was working was not recorded. The average time out of work was from thirteen to fifteen weeks, the longest period being three years

TABLE 3.—*Reasons for Unemployment in Fourteen Cases*

Case	Time Out of Work, Weeks	Reason	Age, Years	Result on Examination
1	52	Inability	69	Marked deformity, with arthritis
2	24	Malingering	40	No arthritis, no marked deformity
3	72	Inability	57	Marked arthritis
4	24	Litigation	25	No arthritis
5	52	Inability	48	Marked arthritis
6	24	Inability	69	Marked arthritis
7	44	Litigation	42	No arthritis
8	24	Compensation	18	No deformity, no arthritis
9	32	Inability	60	Marked arthritis
10	156	Inability (?)	28	Deformity marked
11	24	Litigation	40	Slight arthritis
12	24	Inability	68	Arthritis marked
13	36	Malingering	25	No arthritis, no deformity
14	44	Litigation	57	Moderate arthritis

TABLE 4.—*Extent of Arthritis in One Hundred and Forty Patients*

Extent	Number of Cases	Percentage of Total
Marked.....	22	15
Moderate.....	38	27
Slight.....	14	10
Absent.....	45	32
Not mentioned.....	21	15

and the shortest four weeks. It is interesting to analyze the reasons given for unemployment in the cases of the 14 patients who had not returned to work (table 3). It will be seen that of the 14 patients not working over a long period of time 7 (50 per cent) were actually unable to work, while the remaining 50 per cent were affected by litigation or compensation.

Arthritis was recognized and recorded in 74 cases (approximately 53 per cent, table 4). In most cases in which arthritic changes were found at the follow-up examination, a tendency to generalized arthritis could be demonstrated. Such changes were most marked, as would be expected, in older persons. Injury to, and destruction of, the cartilage of the joint by the force of the fracturing blow was an important factor not alone in causing arthritis but in impeding convalescence and increas-

ing permanent disability. The finger joints,<sup>17</sup> especially the metacarpophalangeal joints, were most affected, and for this reason 11 patients in this series were unable to close their fingers completely.

Injuries to other soft tissues were in general noteworthy by their absence. In only 1 patient was there evidence of any kind of nerve impairment, in this instance, a numbness of the middle finger. There was no example of lasting injury to a blood vessel, and the tendons showed a decrease in function only in proportion to the presence of bony obstruction or arthritic changes.

Subjectively, more or less constant pain of varying degrees of severity was complained of by 41 patients, pain only during changes in the weather by 32, pain only on use by 12, stiffness by 21, weakness by 15 and deformity by 2. Tenderness, located most frequently over the ulnar styloid process was reported by 50 patients and was not noted by the remaining 90. Thirty patients had no complaints, and none were noted in the records of 6.

Fracture of the ulnar styloid process was demonstrated in 101 cases, or 72 per cent, as compared with the 54 per cent reported by Morton,<sup>18</sup> 42 per cent by Beck<sup>19</sup> and only 15 per cent by Braatz.<sup>20</sup> Nonunion was noted in 60 per cent of the cases of fracture of the ulnar styloid process. Grasby and Trick<sup>21</sup> reported nonunion in 50 per cent of their series, showing that in a high percentage of cases fracture of the ulnar styloid process results in nonunion. This probably accounts for the persistent pain and tenderness not infrequently complained of in this region.

That fracture of the intrinsic bones of the carpus as a complication in these cases is unusual is seen from the fact that it occurred in only 1 case (a scaphoid bone) in this series. Edwards and Clayton<sup>22</sup> also reported an incidence of only 1 case in a series of 155.

Open reduction for a serious persistent deformity was required in only 1 case.

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17. Le Breton, P.: Arthritis of the Joints of the Hand Following Colles' Fracture, *Surg. Gynec. & Obst.* 20:450, 1915.

18. Morton, R.: A Radiographic Survey of One Hundred and Seventy Cases Clinically Diagnosed as Colles' Fracture, *Lancet* 1:731, 1907.

19. Beck, C.: Fracture of the Carpal End of the Radius, with Fissure or Fracture of the Lower End of the Ulna and Other Associated Injuries, *Ann. Surg.* 34:249, 1901.

20. Braatz, E.: Der Bruch des Radius am Handgelenk. *Klin.-therap. Wchnschr.* 21:349 and 377, 1914.

21. Grasby, E. D., and Trick, S. P.: An Investigation of the End-Results of Colles' Fracture, *Brit. M. J.* 1:391, 1929.

22. Edwards, H., and Clayton, E. B.: Fractures of the Lower End of the Radius in Adults (Colles' Fracture and Backfire Fracture), *Brit. M. J.* 1:61, 1929.

Objectively, it is interesting to compare a few of the major defects resulting in these cases from the standpoint of anatomy, cosmesis and function. If the anatomic deformity and the cosmetic and functional results are reported in parallel columns, the close relationship between them is striking (table 5).

Since in 139 cases of fracture, or approximately 89 per cent, there was some disturbance in one or more of these groups, it is evident that perfect results following fractures of the wrist are indeed scarce. However, although permanent disability<sup>23</sup> in individual patients ranged from 10 to 90 per cent, the average was only 20 per cent.

TABLE 5.—*Anatomic, Cosmetic and Functional Results in One Hundred and Fifty-Five Cases*

Anatomic Defect	No. of Cases	Cosmetic Result	No. of Cases	Functional Result	No. of Cases
1. Shortening of the radius	122	1. (a) Radial deviation of the hand (b) Prominence of the head of the ulna	120 117	1. (a) Increase in abduction (b) Decrease in adduction	74 72
2. Widening of the wrist joint	116	2. Widening of the wrist joint with increase in its circumference	116	2. (a) Decrease in supination (b) Decrease in pronation	90 13
(a) Widening of the base of the radius	111				
(b) Spreading of the inferior radio-ulnar joint	26				
(c) Intermediate fragment	28				
(d) Lateral splitting of the base of the radius*	106				
3. Tilting of the distal radial fragment	139	3. Angulation of the wrist	121	3. Decrease in gripping power and	112
(a) Posteriorly	118	(a) Silver fork deformity	110	(a) Increase in extension Decrease in flexion	94 113
(b) Anteriorly	21	(b) Flexion deformity	11	(b) Decrease in extension Increase in flexion	6 5

\* The fracture lines were seen in the lateral roentgen view.

Shortening of the Radius:<sup>24</sup> This anatomic deformity was present in all but 33 cases of the series and averaged  $\frac{1}{8}$  inch (0.4 cm.). It is responsible for certain important cosmetic results, such as radial deviation of the hand and prominence of the distal end of the ulna (through leveling of the styloid processes), which in an extreme case give a rather hideous appearance to the extremity. To the same anatomic defect may be traced less important disturbances of function, occurring in abduction and adduction.

23. This is computed on the basis of anatomic, cosmetic and functional results.

24. Boorstein, S. W.: Rational Treatment of Fractures of the Lower End of the Radius, *Am. J. Surg.* 39:50, 1925.

**Widening of the Wrist Joint:** Widening of the base of the radius, spreading of the inferior radio-ulnar articulation and the presence of intermediate fragments and lateral splits, with lateral widening of the base of the radius, are related anatomic deformities which may be grouped together as underlying that cosmetic result so frequently seen, a widened, thickened wrist.<sup>24</sup> They give rise as well to functional disturbances, interference with pronation and supination.

In textbooks and the current literature on these fractures one frequently encounters the statement that widening of the wrist is due to spreading of the inferior radio-ulnar articulation. Yet, in this series of 155 fractures, while widening of the wrist joint with a definite increase in its circumference occurred 116 times (74 per cent), perceptible widening (measurable in fractions of an inch) of the inferior radio-ulnar joint could be demonstrated in only 26 (17 per cent) cases.

Spreading of the inferior radio-ulnar articulation occurred most often in those fractures in which there was no comminution of the distal radial fragment and undoubtedly represented tearing of the inferior radio-ulnar ligaments. However, as the majority of fractures of the base of the radius are comminuted, there is much less likely to be tearing of these ligaments than spreading of the fragments and tearing off of a piece of bone by the ligaments. For example, in 28 cases an intermediate fragment could be demonstrated; apparently the inferior radio-ulnar ligaments had actually pulled off a piece of bone from the base of the radius.

**Tilting of the Distal Radial Fragment:** Posterior tilting of the first degree (on the basis of arbitrary standards already described) was found in 52 cases, of the second degree in 54 cases and of the third degree in 12 cases, making a total of 118 cases, or 76 per cent. In each case there was a silver fork deformity of some degree, with limitation of flexion and usually an increase of extension. Anterior tilting of the first degree was present in 15 cases, of the second degree in 5 cases and of the third degree in 1 case, making a total of 21 cases, or 14 per cent. In each of these there was a varying degree of flexion deformity, with a consequent limitation of extension and an increase of flexion (table 5). Loss of gripping power seemed to result with equal frequency from both anterior and posterior tilting. In 16 cases no tilting could be demonstrated.

#### TREATMENT

In 55 of the 155 cases of fracture the wrist was splinted in acute flexion; in 90, straight out or in slight flexion, and in only 10, in extension. In each case the wrist was held in ulnar deviation. Splints were of molded plaster, anterior and posterior, and were retained for an average of twenty-two days (Kaufman<sup>6</sup>).



In the majority of cases active motion of the wrist was commenced on the ninth day after reduction. In no case was passive motion employed. Motion of the fingers was encouraged from the outset. In 78 cases baking and massage were administered, and in 38 no baking and massage were given, while in 24 cases this treatment was not mentioned.

Treatment had best be considered with regard to immediate care and after-care. Immediate care has to do with reduction of the fracture, the position of the parts following reduction and the application of splints. After-care embraces the period of splinting, the institution of motion, the use of baking and massage and the return of the patient to his work.

Since, as has already been shown, poor functional and cosmetic results are the natural outcome of a faulty anatomic result,<sup>25</sup> the aim of treatment should be to correct and prevent anatomic deformities. This can best be accomplished, first, by gentle and proper manipulation at reduction,<sup>6</sup> with proper anatomic return to normal position and maintenance of that position by splints after reduction (Darrach<sup>26</sup>), and, second, by proper after-care of the fractured part during the period of convalescence, so that anatomic deformities do not increase or recur.

*Immediate Care.*—Reduction: It is generally agreed that these fractures should be reduced as soon as possible.<sup>26</sup> General anesthesia induced by nitrous oxide and oxygen is probably used most frequently. Local infiltration of 1 per cent procaine hydrochloride into the hematoma seems to be satisfactory in selected cases, but it was used only once in this series.

Reduction should be accomplished with the least possible trauma,<sup>26</sup> as each additional trauma along the line of fracture causes an increase in the extent of the zone of bone injury and hence increases the chance of anatomic deformity. Impaction should not be broken up roughly by rocking the fragments vigorously back and forth on each other. Neither should the fragments be jammed tightly into each other for the so-called reimpaction.

Molding of the fragments at the time of reduction is important. Lateral pressure exerted from both sides simultaneously, with pressure from the front and the back, will reduce the tendency of the distal radial fragment to mushroom and slip out of place. This is especially true when there is comminution.

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25. Lacroix, P. G., and Cohn, I.: Fractures of the Base of the Radius: Method of Treatment and End Results, New Orleans M. & S. J. 77:425, 1925.

26. Darrach, W.: Fractures of the Lower Extremity of the Radius: Diagnosis and Treatment, J. A. M. A. 89:1683 (Nov. 12) 1927.

**Position of the Parts Following Reduction:** The proper position in which to place the fractured parts seems clear enough if the underlying pathologic change is understood. As has been shown, in the usual fracture the zone of bone injury is triangular, with its base toward the dorsum of the wrist. Thus there is at the site of fracture a wedge of injured bone which must be absorbed and replaced by new bone and which may collapse if the hand is put in extension, causing a recurrence of the initial deformity. Further, it can be shown that jamming the hand down into acute flexion changes the shape of the zone of bone injury, increases the extent of bone injury, tends to increase radial shortening and may give rise to a permanent flexion deformity. Therefore, an intermediate position of slight flexion seems best, as advocated by Edwards and Clayton,<sup>27</sup> Ely<sup>27</sup> and Abbe.<sup>28</sup> The hand should then be carried into ulnar deviation to approximate the fragments of the ulnar styloid process (when it is fractured) and to take the pressure of the hand off the line of fracture. Rather marked supination is also favored, to guard against the loss of supination as well as to lessen the pull of the extensor muscle,<sup>29</sup> which tends to tip the distal fragment of the radius posteriorly. For example, with the hand in pronation and with the splints reaching only to the elbow there is a tendency for the biceps muscle to supinate the proximal fragment of the radius, union then occurring with the distal fragment in pronation and the proximal fragment in supination.

**Splints:** An anterior and a posterior molded plaster of paris splint should be used. They are easy to make, can be applied quickly and can be molded to the individual patient; besides, the wrist can better be held in its corrected position while the splints are being applied than during the application of circular plaster. Wood or metal splints cannot be molded to the patient as well as plaster. Subsequent increase or diminution in swelling of the soft parts can be accommodated merely by rebandaging the splints.

The anterior splint should reach distally to the crease in the palm of the hand, sometimes referred to as the head line, which indicates anteriorly the metacarpophalangeal joints. This splint should run proximally to just below the elbow joint. The posterior splint should begin at a distal level behind the knuckles and extend proximally above the elbow, in order to give good support to the hand and to the distal fragment of the radius, thus removing pressure from the line of fracture and preventing shortening. In this way, too, the fragments can be kept

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27. Ely, L. W.: Colles' Fracture, with a New Theory of Its Mechanism, *J. A. M. A.* 50:2130 (June 27) 1908.

28. Abbe, R.: Colles' Fracture, *Internat. Clin.* 4:209, 1893.

29. Brown, A. J.: The Treatment of Colles' Fracture Considered from the Standpoint of Muscle Physiology, *Am. J. Surg.* 31:122, 1917.

properly apposed in supination (Darrach). Free active motion of the finger joints, especially of the metacarpophalangeal joints, is thus assured.

*After-Care.*—Period of Splinting: It has been shown by Leriche<sup>30</sup> that the period of maximum absorption and brittleness in a knitting fracture is from the second to the third week. This may be termed the critical period, for clinically it is the time when complete redispacement<sup>31</sup> is most likely to take place in those cases in which protection is insufficient. These fractures should therefore be protected by splints for a period of three weeks in patients 30 years of age or younger; in patients beyond that age four weeks should be adhered to as a period of protection against the recurrence of deformity. Edwards and Clayton,<sup>32</sup> Kaufman<sup>6</sup> and Adams<sup>1</sup> advised similar periods of protection by splints.

*The Institution of Motion:* Within the past ten years active and passive motion as early as forty-eight hours after reduction of fracture of the wrist has been advocated. But it is well to consider carefully the pathologic change underlying such injuries; any pressure on the line of fracture, especially during the critical period, will surely cause anatomic shortening and spreading of the comminuted fragments.

Lucas-Champonnière<sup>32</sup> is perhaps quoted most frequently on this point, yet in his original article the cases were carefully selected, and it was only in the case of the simplest fracture without displacement that he started motion as early as the second day. With a severely comminuted fracture he immobilized the wrist for a longer period without active motion. In all cases he exercised great caution in having the patient move the fractured part. There are undoubtedly a few selected cases in which motion at the wrist joint could be started as early as in forty-eight hours, but it is a much safer general rule to keep the joint immobile and protected for three weeks.

Motion of the fingers,<sup>33</sup> however, is another matter. Constant active motion from the outset is essential to a good result. It acts as a massage to the fingers, stimulating the circulation, maintaining the tone of the nerves and preserving the nutrition of the tissues. With regard to proper function, the metacarpophalangeal joints are the most important joints in the hand, and during the period of convalescence every effort

30. Leriche, R.: *Physiology of Bone*, St. Louis, C. V. Mosby Company, 1928, p. 139.

31. This took place in 6 cases of fracture in this series and is therefore an actual menace.

32. Lucas-Champonnière, J.: *Thérapeutique des fractures de l'extrémité inférieure du radius*, J. de méd. et chir. prat. **79**:129, 1908.

33. Goretzky, P.: *Ein Beitrag zur Behandlung der Radiusbrüche im unteren Drittel*, Deutsche Ztschr. f. Chir. **205**:285, 1927.

should be made to preserve their flexibility. In the final analysis, the function of the fingers is the most important part of the end-result and should always be kept in mind.

**The Use of Baking and Massage:** After removal of the splints at the end of three or four weeks, baking and massage may be begun. But the value of this treatment is frequently overrated. Active motion is likely to be productive of much more satisfactory results. The baking and massage cause transient hyperemia and a feeling of well-being for several hours, after which the part becomes cold and the reaction of stiffness sets in. Constant active motion and slight use of the hand at this time give a continuous and more physiologic massage, normal function being restored much more quickly. The patients in this series who were treated by active motion alone seemed to recover more rapidly than those who received baking and massage, although no definite statistics can be given.

**The Return of the Patient to Work:** In this series the average time lost from work was thirteen and five-tenths weeks, which coincides closely with the experience of Eliason.<sup>14</sup> As a rule, approximately three months should elapse before a man returns to heavy manual labor. Light work, however, may be resumed in two months, usually with considerable benefit. All symptoms that are going to clear up, such as stiffness, pain and limited motion, usually disappear in the first twelve months. All symptoms persisting beyond this period should be considered permanent.

#### SUMMARY

A series of 155 cases of fracture of the base of the radius by indirect violence in 140 adults, all examined by me on an average of sixteen months after reduction, are analyzed as to etiology, pathologic change, treatment and end-results.

Shortening of the radius averaging  $\frac{1}{6}$  inch occurred in 78 per cent of the cases.

Widening of the wrist joint was seen in 75 per cent. In most cases it was due not to spreading of the inferior radio-ulnar articulation but to an actual increase in the width of the base of the radius.

Tilting of the distal radial fragment posteriorly occurred in 76 per cent of the cases, and anteriorly in 14 per cent. and comminution of this fragment was present in 68 per cent.

Fracture of the styloid process of the ulna was noted in 72 per cent, in 60 per cent of which nonunion was noted.

Fracture of the carpal bones was rare, 1 case only (of a scaphoid process) occurring in this series.

Permanent injury to soft tissues was practically nonexistent.

In 90 per cent of the cases there was evidence of some defect in the anatomic, cosmetic or functional results to greater or less degree.

Cosmetic and functional pathologic changes, when present, could always be traced directly to an underlying anatomic deformity.

The length of disability averaged three months, and most patients were able to return to their previous occupations.

The average permanent disability was approximately 20 per cent, ranging from 10 to 90 per cent in individual cases.

A simple and reasonably accurate method of roentgen measurement of anatomic deformities resulting from these fractures has been devised and is herewith presented.

A short and convenient classification of such fractures is suggested, based on the direction of the lines of fracturing force.

#### CONCLUSIONS

1. In cases of fracture of the base of the radius by indirect violence in adults, the manner of reduction and the position in which the fragments are to be held after reduction should be determined only after careful study of the pathologic changes in the bone, as shown by the roentgenogram in each individual case. This should include (*a*) consideration of the zone of bone injury, that is, actual and potential destruction of bone, and (*b*) actual mensuration of existing anatomic deformities of bone for purposes of record and subsequent comparison.

2. Treatment should be directed toward the prevention of functional and cosmetic failure through the correction and prevention of anatomic deformity. This is best accomplished in most cases by (*a*) putting the hand in slight flexion, ulnar deviation and supination, with volar and dorsal splints, the latter to extend above the elbow, (*b*) immobilizing the wrist joint for three or four weeks but maintaining active motion of the fingers from the time the splints are applied and (*c*) checking up by roentgenogram two or three weeks after reduction, as lines of comminution stand out most clearly at this time.

# SURGICAL AND ANESTHETIC RISK IN CARDIAC DISEASE

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The diversity of opinion in regard to whether or not patients with cardiac disease are good risks for surgical procedures or anesthesia has prompted the present study of the postoperative course in 336 patients with this disease who came to the operating room during a two year period.

In medical textbooks the following statements appear: "Serious uncompensated valvular disease of the heart is a contraindication to general anesthesia."<sup>1</sup> "If loss of compensation is present . . . pulmonary anesthetics should be avoided and local or spinal anesthesia used."<sup>2</sup> "General anesthesia is contraindicated in patients with grave cardiac or kidney disease."<sup>3</sup>

Several authors, including Harvey,<sup>4</sup> who wrote an excellent article on the subject, have studied the cardiac reserve in cases of various types of cardiac lesions and advise as to diagnosis and treatment. No attempt will be made in this paper to elaborate on this phase of cardiac disease.

Necropsy on 77 patients who died consecutively after operation at the Billings Hospital revealed only 1 case of heart failure, 1 case of coronary thrombosis and 4 cases of bronchopneumonia (table 1). This would tend to indicate that the percentage of postoperative deaths due to cardiac disease is relatively low.

The cases of 50 patients with severe cardiovascular disease in which major operations were performed were reviewed (table 2). Although 28 of these patients showed decompensation before operation, there

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From the Department of Surgery, the University of Chicago Clinics.

1. Warbasse, J. P.: *Surgical Treatment*, Philadelphia, W. B. Saunders Company, 1920, vol. 1, p. 92.

2. Gwathmey, J. T.: *Anesthesia*, ed. 2, New York, The Macmillan Company, 1929, p. 324.

3. Eliason, E. L.; Ferguson, L. K., and Lewis, E. K.: *Surgical Nursing*, Philadelphia, J. B. Lippincott Company, 1929, p. 101.

4. Harvey, S. C.: *The Complications in Surgery: Their Prevention and Treatment*, in Nelson Loose-Leaf Living Surgery, New York, Thomas Nelson & Sons, 1927, vol. 1, chap. 10, p. 571.

were no deaths due to cardiac disease and only 1 patient had mild post-operative decompensation. This patient had a history of angina.

The findings just given stimulated interest in making a detailed study of the immediate and postoperative reactions to anesthesia and operation of 336 consecutive patients with cardiac disease in a series of 6,800 who were operated on (table 3). Approximately two thirds of this group of patients with cardiac disease underwent major operations. It is appreciated that the classification of cardiac disease used is very generalized, and that some of the groups are entirely too small for a statistical study to be very valuable; however, we believe that the data give some indication of the mortality rate in the various diseases.

TABLE 1.—*Deaths Due to Cardiac Disease and Pulmonary Complications in Seventy-Seven Patients at the Billings Hospital Who Died Consecutively After Operation*

Cause of Death	Number of Cases
Heart failure.....	1 (prostatectomy)
Coronary thrombosis.....	1
Bronchopneumonia.....	4

TABLE 2.—*Data for Fifty Cases of Severe Cardiovascular Disease in Which Major Operations Were Performed*

Complications	Number of Cases
Decompensation before operation.....	28
Compensation before operation.....	22
Intestinal obstruction fourteenth day after operation (mechanical).....	1
Severe infection of wound, septicemia, uremia (no albuminuria before operation)	1
Mild decompensation after operation (history of angina).....	1

#### HYPERTENSIVE AND ARTERIOSCLEROTIC HEART DISEASE

There is some diversity of opinion concerning the operative risk in patients with this type of heart disease. Sprague<sup>5</sup> found his greatest mortality in this group. In his series of 75 patients with arteriosclerotic and hypertensive heart disease there were 24 deaths, one half of which were due to cardiac failure. On the other hand, Butler, Feeney and Levine<sup>6</sup> stated that hypertension does not materially increase the operative risk. They found a mortality of 7.3 per cent in 146 patients with a systolic pressure over 160 mm., as opposed to a 5.9 per cent mortality among 245 patients with pressure below 160 mm. They stated

5. Sprague, H. B.: *The Heart in Surgery*, Surg., Gynec. & Obst. **49**:54 (July) 1929.

6. Butler, S.; Feeney, N., and Levine, S.: *The Patient with Heart Disease as a Surgical Risk*, J. A. M. A. **95**:85 (July 12) 1930.

that in general patients with very high blood pressures are good surgical risks.

*Hypertension.*—O'Hare and Hoyt<sup>7</sup> considered the patient with hypertension a fair risk provided there is no associated renal lesion. They stressed the importance of careful following of the blood pressure during operation, the control of bleeding and the early use of fluids and stimulants if indicated.

TABLE 3.—Data for 336 Consecutive Patients with Heart Disease in a Series of 6,800 Operated On

Diagnosis	Num- ber of Pa- tients	Poor Recov- ery	Died	Deaths Due to Cardiac Disease		Deaths Due to Pulmonary Disease		Deaths Due to Combined Cardiac and Pulmo- nary Disease	Deaths Due to Other Causes	
				Hos- pital	Home	Hos- pital	Home		Hos- pital	Home
Hypertension.....	91	23	10	2 (spinal anes- thesia)	1 (spinal anes- thesia)	1 due to aspira- tion)	2	..	3	2
Compensated valvular lesions	60	14	1	..	..	..	..	..	1	..
Compensated myocardi- al disease	44	11	4	..	..	3	..	1 + renal infection (spinal anesthesia)	..	..
Thyrotoxic heart dis- ease	36	19	3	1	..	..	..	1	1	..
Decompensation (not thyroid)	20	9	5	1 (spinal anesthesia)	1	1 (embolus)	..	1	1	..
Arteriosclerotic heart disease	18	6	3	..	..	..	..	..	3	..
Congenital heart dis- ease	10	1	0	..	..	..	..	..	..	..
Coronary occlusion....	8	5	1	1	..	..	..	..	..	..
Heart block.....	4	0	0	..	..	..	..	..	..	..
Angina pectoris.....	3	2	1	1	..	..	..	..	..	..
Acute pericarditis.....	1	1	1	1	..	..	..	..	..	..
Miscellaneous lesions...	31	7	2	..	..	..	..	..	2	..
Total.....	336	95	31	7	2	6	..	3	11	2
Major operations.....	231									
Minor operations.....	105									

McQuiston and Allen at the Mayo Clinic<sup>8</sup> studied 350 patients with definite hypertension who underwent major surgical operations. In the majority of these patients myocardial function was normal or nearly so. The operative mortality in this group was 2.6 per cent, which was

7. O'Hare, J. P., and Hoyt, L.: *Surgery in Nephritic and Hypertensive Patients*, New England J. Med. 200:1292, 1929.

8. McQuiston, J. S., and Allen, E. V.: *The Relationship of Arterial Hypertension to Surgical Risk*, in *Collected Papers of the Mayo Clinic*, Philadelphia, W. B. Saunders Company, 1932, vol. 24, p. 467.



approximately the same as in a group of unselected patients undergoing the same procedures. Death occurring chiefly as the result of hypertension was observed only 3 times, giving an incidence of 0.86 per cent. The authors conclude from this study that patients with hypertension without obvious or with mild myocardial and renal insufficiency tolerate major surgical operations very well.

Since many of the patients in this class are elderly persons, the importance of age in increasing the surgical risk must be considered. Butler, Feeney and Levine stated: "We may conclude that patients with heart disease demonstrate the general rule that increasing age produces an increase in surgical mortality." Lidwill<sup>9</sup> stated that elderly patients who show no definite abnormality on physical examination may be very dangerous subjects for general anesthesia. He finds that they tend to die on the operating table and have little power of recovery.

In this series there were 91 patients with hypertension with a minimum systolic pressure of 170 mm. of mercury, a maximum of 252 mm. and an average of 195 mm. Thirty-seven of these had a systolic blood pressure above 200 mm. There were 47 males and 42 females in the group. Sixty-four of the patients were over 50 years of age, with the incidence in age groups as follows: from 51 to 60, 20 patients; from 61 to 70, 29; from 71 to 80, 13, and from 81 to 90, 2. There were 64 major and 27 minor operations. Among these patients there were 10 deaths, or a mortality of 10.9 per cent. Thirteen patients had poor recovery. There were 3 deaths due to cardiac disease, none of which took place immediately after operation. These 3 patients had received spinal anesthesia. There were 2 deaths from pulmonary complications. One death from bronchopneumonia occurred a few days postoperatively after local plus ethylene-oxygen anesthesia. The other death from pulmonary disease took place seventeen days after operation and was due to aspiration from an ulcerating carcinoma of the esophagus. The patient had had a cannula gastrostomy under local plus ethylene-oxygen anesthesia. The 5 other deaths were from causes unrelated to the cardiac or pulmonary system.

There were 5 patients with cardiac complications with poor recovery (table 4). One of these patients was a woman who had a retrogasserian neurectomy in the sitting position under local plus nitrous oxide-oxygen anesthesia. This patient's condition was poor during operation, with a falling blood pressure and rapid, weak pulse. On the fifth postoperative day she had an anginal seizure, which was her first attack of this nature. A patient with a history suggesting possible coronary involvement had a definite coronary thrombosis after thyroid-

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9. Lidwill, M. C.: Cardiac Disease in Relation to Anesthesia, *Anesth. & Analg.* 9:145 (July-Aug.) 1930.

ectomy. The other 3 patients had laparotomies under ethylene-oxygen plus ether anesthesia, and all of them showed auricular fibrillation for two to three days after operation.

Five patients had pulmonary complications with recovery. Twenty-four hours after osteoplastic exploration and decompression, pneumonia developed in a patient who had been in very poor condition preoperatively. Bronchopneumonia developed in a man, 85 years of age, seven days after cheiloplasty and excision of the submaxillary glands for carcinoma of the lip, the operation having been performed under local anesthesia. A patient who had an appendectomy under ethylene-oxygen anesthesia had râles and fever on the fourth and fifth days. Atelectasis followed by bronchopneumonia bilaterally occurred in a patient who had a ventral hernia repaired under spinal plus ethylene-

TABLE 4.—*Postoperative Complications with Recovery*

Diagnosis	Number of Cases	Cardiac Complications	Pulmonary Complications	Combined Cardiac and Pulmonary Complications	Other Types
Hypertension.....	91	4	5	..	4
Compensated valvular lesions.....	60	3	2	..	5
Compensated myocardial disease.....	44	3	2	..	2
		(spinal anesthesia)			
Thyrotoxic heart disease.....	36	9	2	1	4
Decompensation (not thyroid)....	50	2	..	..	2
Arteriosclerotic heart disease.....	18	..	1	..	2
Congenital heart disease.....	10	1	..	..	..
Coronary occlusion.....	8	4	..	..	..
Heart block.....	4	..	..	..	..
Angina pectoris.....	3	1	..	..	..
Acute pericarditis.....	1	..	..	..	..
Miscellaneous lesions.....	31	..	..	..	..
Total.....	336	28	12	1	27

oxygen anesthesia. The findings in the chest in a patient who underwent nephrectomy under ethylene-oxygen anesthesia suggested atelectasis or pneumonia.

**SUMMARY.**—Thus it may be seen that among 91 patients with hypertension there were only 3 deaths due to cardiac disease. Each of these 3 patients was classed as a poor operative risk. Spinal anesthesia was employed. One patient died of cardiac failure several days after operation. Another patient died of cardiac failure several weeks after being discharged. The third death was due to terminal cardiac dilatation after the patient had successfully recovered and been discharged and then readmitted some weeks later. Some authors, perhaps, would class all 3 of these deaths as due to spinal anesthesia.

**Arteriosclerosis.**—There were 18 patients with arteriosclerosis. The maximum age was 86, the minimum 49 and the average 67. There were 16 males and 2 females in this group. Eleven major and 7 minor operations were performed. There were 3 deaths (16.6 per cent mor-

tality), all of which occurred many days after operation and from causes unrelated to the cardiac or pulmonary system. One patient made a poor recovery when atelectasis developed following ether anesthesia.

**SUMMARY.**—Although 3 of 18 patients with arteriosclerotic heart disease died, none of the deaths was due to heart disease. In no instance was there an aggravation of the preexisting heart disease.

*Type of Anesthesia.*—The best type of anesthesia to employ in cases of hypertension or arteriosclerosis has been much discussed. Many persons consider local anesthesia the method of choice, particularly for patients with arteriosclerosis. Horine<sup>10</sup> stated that general anesthesia may be used in many cases if all cyanosis is avoided but that local anesthesia is preferable, especially if there is any evidence of congestive heart failure or anginal pain. He warned against the use of chloroform or spinal anesthesia because of the marked fall in blood pressure accompanying the use of these agents, with frequently resulting cerebral anemia. He stated that local anesthesia is the only method permissible for patients with arteriosclerosis and associated coronary involvement. Horine urged also that no ephedrine or epinephrine be used in the local solution, for two reasons: first, because of the tachycardia which follows the sympathetic stimulation, and, second, because of the possibility of vasoconstriction with an elevation of blood pressure which may produce coronary thrombosis. This is also a factor to be considered in spinal anesthesia, since ephedrine is customarily employed with this type of anesthesia. It is important to avoid excitement during the period of induction, since Hewitt<sup>11</sup> reported cases of cerebral hemorrhage resulting in patients with arteriosclerosis who struggled during anesthesia.

For the patients with arteriosclerosis the types of anesthesia used were: local, in 9 cases; spinal, in 5 cases, and ethylene-oxygen plus ether and nitrous oxide-oxygen in 1 instance each.

For the patients with hypertension the anesthetics were as follows:

Ethylene-oxygen .....	29
Local .....	28
Spinal .....	10
Ethylene-oxygen plus ether.....	10
Local plus ethylene-oxygen.....	3
Nitrous oxide-oxygen.....	3
Spinal anesthesia plus ethylene-oxygen.....	2
Nitrous oxide-oxygen plus local.....	2
Ethylene-oxygen and ether (drop).....	2
Ether, caudal and sacral.....each	1

10. Horine, E. F.: Anesthesia in Heart Disease, *Anesth. & Analg.* **13**:129 (May-June) 1934.

11. Hewitt, F. W.: *Anesthetics*, ed. 4, New York, The Macmillan Company, 1912, p. 142.

Ethylene-oxygen and local anesthesia were most frequently employed. Ethylene-oxygen anesthesia was used alone, with local anesthesia or with small amounts of ether. In the patients receiving these types of anesthesia there was only 1 bad result, namely, in the patient in whom coronary thrombosis developed two days postoperatively. The results seem to justify the conclusion that the use of ethylene and oxygen is not contraindicated for these patients.

#### COMPENSATED VALVULAR LESIONS

The presence of compensated valvular defects seems to add little to the surgical risk, according to George and Louis Herrmann.<sup>12</sup> Butler, Feeney and Levine<sup>6</sup> reported 10 deaths in a series of 120 patients, a mortality of 8.3 per cent.

The results in this series of 60 patients with compensated organic valvular lesions seem to substantiate the belief of previous authors that these patients are good surgical risks.<sup>13</sup> There was 1 death, a mortality rate of 1.6 per cent. This patient died three days after operation for a ruptured appendix and peritonitis. The cause of death was unrelated to the pulmonary or cardiac systems. There were 39 female and 21 male patients in this series. Thirty of the operations were major, and 30 were minor.

The ages varied from 3 to 54 years, the average age being 25. A wide variety of types of anesthesia were used: ethylene-oxygen in 13 operations; local, in 12; nitrous oxide-oxygen, in 11 (8 of these were minor operations); ether, in 10; ethylene-oxygen plus ether, in 8; ethylene-oxygen plus ether (open drop), in 4; spinal, in 1, and nitrous-oxide oxygen and ethylene-oxygen, in 1.

Three patients in this group had cardiac symptoms postoperatively during recovery. One showed fibrillation for a day after receiving ethylene and oxygen plus ether for an abdominal hysterectomy. Another patient (a man of 44) had fibrillation lasting four days after receiving nitrous-oxide and oxygen for an open reduction of a fractured tibia and fibula. One child had symptoms of acute cardiac dilatation for a few days after receiving ether for the open reduction of a hip.

Two patients had pulmonary complications during recovery. One child recovering from scarlet fever had pneumonia two days after receiving nitrous-oxide and oxygen for a myringotomy, and one 36 year old woman with preoperative sibilant râles had a cough for a few days after receiving ethylene and oxygen for repair of an eventration.

12. Herrmann, G., and Herrmann, L.: Cardiac Disorders in Surgical Patients: Criteria Used in Estimating the Risk Involved. *Texas State J. Med.* **30**:183 (July) 1934.

13. Blackford, J. M.; Willins, F. A., and Haines, S. B.: Operative Risk in Cardiac Disease, *J. A. M. A.* **69**:2011 (Dec. 15) 1917.

SUMMARY.—Thus, in a group of 60 patients with compensated valvular lesions there was but 1 death, and this was unrelated to the cardiovascular system. Three patients had postoperative cardiac symptoms, with recovery.

#### COMPENSATED MYOCARDIAL DISEASE

Patients with compensated myocardial disease are generally believed to tolerate operations rather well. Butler, Feeney and Levine<sup>6</sup> report a 6.6 per cent mortality for this condition. In the present series of 44 cases there were 4 deaths, a mortality of 9 per cent. There were no deaths from cardiac disease. The 4 deaths occurred from three to five weeks postoperatively. Two of the patients had carcinoma and died of terminal bronchopneumonia five weeks after operation. One, a patient with carcinoma of the stomach, died of peritonitis, subdiaphragmatic abscess and multiple pulmonary abscesses after 2 operations under local anesthesia for suture of a duodenal fistula, and 1 died of bilateral pyelonephritis and retroperitoneal abscess three weeks after receiving a spinal anesthetic for a partial nephrectomy and decapsulation nephrotomy.

The average age of the patients was 52 years. Twenty-nine were females, and 15 were males. Thirty-one major and 13 minor operations were performed. A variety of types of anesthesia was employed: ethylene-oxygen, in 12 operations; local, in 11; ether, in 3; spinal, in 3; nitrous oxide-oxygen, in 5 (4 of these were minor operations); ethylene-oxygen plus ether, in 6; ethylene-oxygen plus local, in 3, and ethylene-oxygen plus ether (drop), in 1.

There were 3 cardiac and 2 pulmonary postoperative complications in the group that recovered. A man of 64 had a variable blood pressure and fibrillation for seven days after receiving ethylene and oxygen plus ether for an exploratory laparotomy and removal of material for biopsy from a retroperitoneal tumor. A woman of 30 had cyanosis and fibrillation for several minutes after receiving a spinal anesthetic. A woman of 54 had a rapid weak pulse and dependent edema for several days after receiving a local anesthetic plus ethylene and oxygen for a subtotal gastrectomy.

In regard to the postoperative pulmonary complications, 1 patient had atelectasis two days after receiving ethylene and oxygen plus ether for repair of a ventral hernia, and a patient with alcoholism had a cough for three days after receiving ethylene and oxygen and ether for a cholecystectomy.

SUMMARY.—Of 4 deaths in 44 cases of compensated myocardial disease, none was attributed to the cardiovascular system. Three patients had cardiac symptoms during recovery from major operations, 1 having received a spinal anesthetic.

## THYROTOXIC HEART DISEASE

Patients with thyrotoxic heart disease have frequently been thought to be very poor risks. However, in recent years, with improvement in medical and surgical management, the danger has been much reduced. Lahey<sup>14</sup> reported a mortality of 3.6 per cent among 138 patients. Herrmann and Herrmann<sup>12</sup> stated that heart disease of thyrotoxic origin has a less serious surgical significance than either rheumatic or arteriosclerotic heart disease. In Sprague's<sup>5</sup> 14 cases there was only 1 death in the hospital. Ramsey<sup>15</sup> emphasizes the importance of careful supervision of these patients both before and after operation.

There were 36 patients with thyrotoxic heart disease in this series. There were 3 deaths, a mortality of 8.3 per cent. Twenty-seven of the patients were females, and 9 were males, with a range in age of from 14 to 70 years and an average age of 48. Seven of these patients had auricular fibrillation when they came to the operating room but were not bad risks. Of these 7, 3 had received digitalis preoperatively. Five of the patients with thyrotoxic heart disease had marked cardiac failure preoperatively. Four of these received digitalis before operation. The fifth patient did not receive digitalis, and she had an excessively stormy convalescence. All the patients with thyroid disease had received compound solution of iodine U. S. P. before operation.

A woman of 26 who had a thyroidectomy with ethylene-oxygen anesthesia died on the day of operation from tracheal compression due to hemorrhage. A woman of 42 who was operated on under local anesthesia died two days later of an "asthenic reaction to thyroidectomy." The third death followed thyroidectomy in a man of 59, who succumbed to cardiac failure and pneumonia seven days after operation.

Ten patients showed cardiac symptoms after thyroidectomy. One of these was a woman, 62 years old, who had an unusually severe reaction. It was believed that in this instance operation should have been delayed until the patient was digitalized. Five patients had auricular fibrillation for from twenty-four to forty-eight hours after operation under ethylene-oxygen anesthesia. Two men had very severe crises following thyroidectomy with local anesthesia. A patient with previous disease of the coronary arteries had an attack of coronary thrombosis after operation. The 2 pulmonary complications were persistent coughs for several days after operation.

The necessity of caring for a patient with thyrotoxicosis before surgical procedures are instituted is strikingly demonstrated in chart 1,

14. Lahey, F. H.: *Hyperthyroidism Associated with Cardiac Disorders*, Surg., Gynec. & Obst. 50:139 (Jan.) 1930.

15. Ramsey, R. A.: *The Behaviour of the Heart Under Nitrous Oxid-Oxygen Anesthesia*, Anesth. & Analg. 9:33 (Jan.-Feb.) 1930.

which illustrates a case not in this series. The severe reaction following cholecystectomy and gastro-enterostomy for a badly infected gallbladder and a gastric ulcer in a woman with thyrotoxicosis in all probability would have been obviated had it been possible to have treated the thyroid condition first. Unfortunately, cholecystectomy was not the operation of choice in this case.

Many authors have advised the use of local anesthesia for the patient with thyrotoxicosis with cardiac damage. Horine<sup>10</sup> stated that it is the method of choice unless the patient is unduly apprehensive, in which

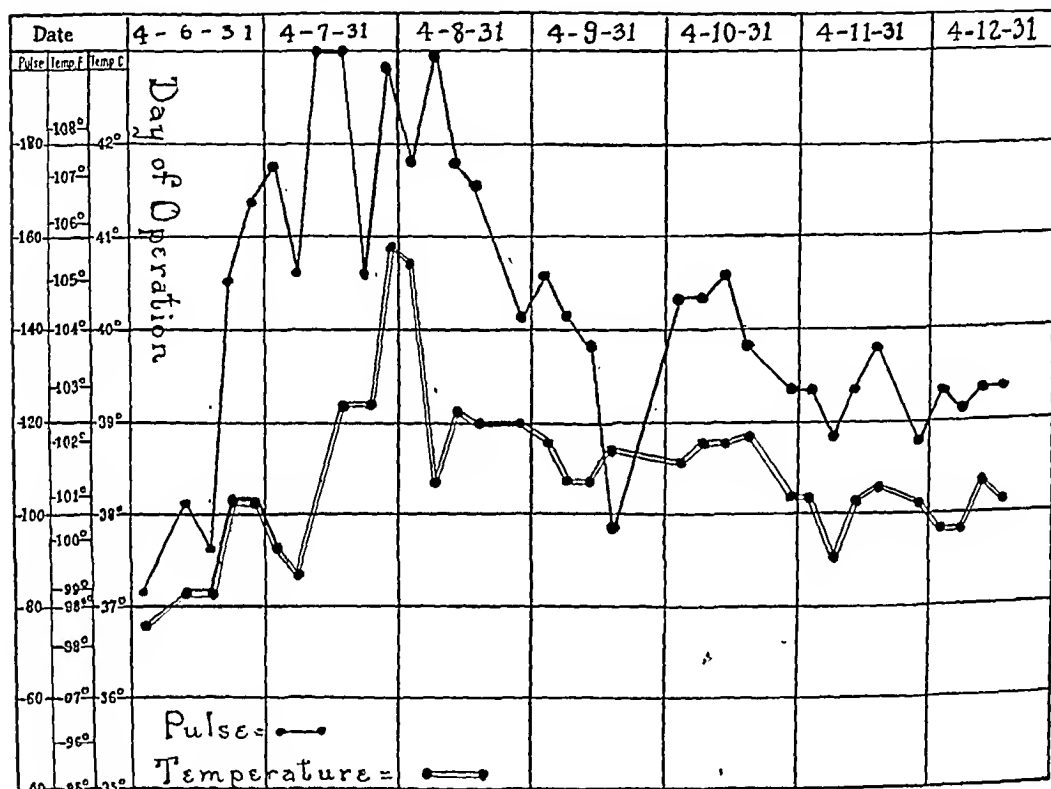


Chart 1.—Record of the postoperative course of a patient with cardiac disease complicated by thyrotoxicosis.

case an inhalation anesthetic must be given. He believes that auricular fibrillation in these patients is not the contraindication to general anesthesia that it is in patients with rheumatic heart disease. Ramsey<sup>15</sup> recommended that nitrous oxide and oxygen be employed but stressed the need for a high concentration of oxygen. He observed marked dilatation of the right heart during operation in patients who had insufficient oxygen with nitrous oxide anesthesia, but by avoiding all cyanosis he can safely administer this agent. Lahey<sup>14</sup> advised the use of ethylene and oxygen in all cases unless the blood pressure is markedly elevated. He found it as safe and more satisfactory to the patient than

local anesthesia. In this series ethylene-oxygen anesthesia has been most frequently used. Twenty-five patients received ethylene-oxygen and 7 local anesthesia, while in 4 cases ethylene-oxygen and local anesthesia were combined. Ethylene-oxygen anesthesia has been found very satisfactory in such cases and appears superior to nitrous oxide-oxygen anesthesia because of the higher percentages of oxygen which may be administered.

SUMMARY.—Thus, 1 death in a series of 36 patients with thyrotoxic heart disease who underwent operation is considered a postoperative death due to cardiac disease. This patient died of so-called "asthenic reaction to thyroidectomy" two days after having had a thyroidectomy under local anesthesia. Since the chart is not complete, this may not have been a death due to cardiac disease. One patient, a man of 59 years, died of cardiac failure and pneumonia seven days after operation under local anesthesia. He was a poor surgical risk, with auricular fibrillation, myocardial insufficiency and generalized arteriosclerosis. Treatment with digitalis was started four days before operation and continued postoperatively. The postoperative course was not alarming until the fifth postoperative day.

Since 9 patients had cardiac and 1 patient had cardiac and pulmonary complications after operation, it is obvious that postoperative cardiac symptoms not infrequently occur in patients with thyrotoxic heart disease.

Proper preoperative medical management of thyrotoxic heart disease is apparently an important factor in decreasing the postoperative morbidity rate.

#### DECOMPENSATION (NOT DUE TO THYROID DISTURBANCE)

Cardiac decompensation is generally believed to increase the danger of operation. Herrmann and Herrmann<sup>12</sup> stated: "Congestive heart failure . . . must be considered as definitely contraindicating surgical treatment in anything except the most urgent emergencies."

Butler, Feeney and Levine<sup>6</sup> reported a series of 50 operations on 50 patients with congestive heart failure, with a mortality of 17.1 per cent.

In this series there were 30 patients with congestive heart failure preoperatively. Of this number, 4 died, giving a mortality of 13.3 per cent. There were 18 males and 12 females in this group. Twenty-three major and 7 minor operations were performed. The maximum age was 78 years, and the minimum 43, with an average of 62. The types of anesthesia used for the entire group were: ethylene-oxygen, in 13 cases; local, in 12; spinal, in 2; ethylene-oxygen plus ether, in 2, and sacral, in 1.



The 4 deaths were not all of cardiac nature. A man of 68 had fibrillation preoperatively, with râles in the chest and a basal metabolic rate of  $+28$ . He received digitalis and compound solution of iodine U. S. P. for three days before the second stage of a prostatectomy under spinal anesthesia, and the administration of digitalis was continued after operation. He died four days later of cardiac failure. An attempted suprapubic prostatectomy in a 78 year old man was followed thirty-seven days later by death from carcinoma of the prostate and obstruction of the urinary tract. A 55 year old man had a partial prostatectomy and insertion of radium with ethylene-oxygen plus ether anesthesia. Four days postoperatively myocardial failure developed, and he died six weeks later with metastases of carcinoma to the pelvis and neck and terminal bronchopneumonia. There had been no preoperative administration of digitalis in this case. The fourth death occurred in a 67 year old man who had a transurethral electro-

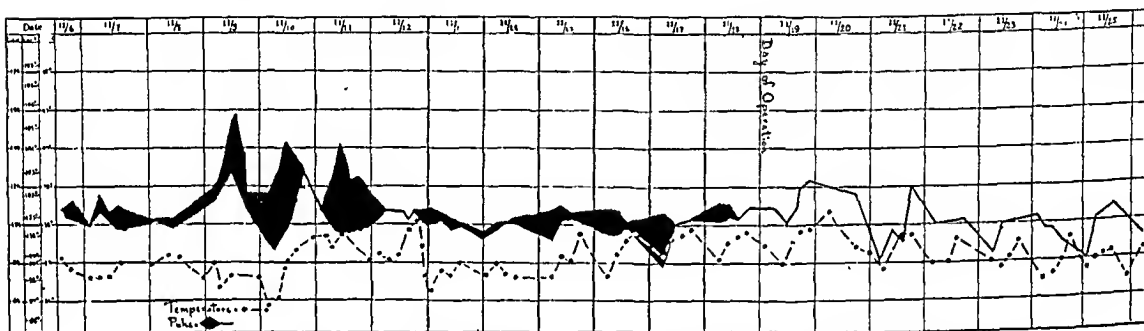


Chart 2.—Record of the preoperative and postoperative course of a patient with severe decompensation.

resection of the prostate under spinal anesthesia. This patient did not receive any cardiac therapy either preoperatively or postoperatively. He was apparently making a good recovery and had been allowed to be up in a chair for several days before death occurred suddenly from a pulmonary embolus.

Chart 2 illustrates the course following amputation of the midportion of the thigh of a middle-aged woman with severe decompensation. This patient entered the hospital with severe decompensation of some duration. She was given digitalis, and on the thirteenth day of hospitalization fibrillation ceased. The following day operation was performed under ethylene-oxygen anesthesia. The recovery was uneventful.

Chart 3 illustrates a case not in this series but is presented because it represents an extreme degree of preoperative decompensation. This illustration was lent by Dr. Edmund Andrews. Mrs. C. B. was a middle-aged woman who for twenty years had been bedridden with far advanced myocardial failure, and her demise had been expected at

any time during this period. She suffered from a ruptured appendix. Figure 7 shows the uneventful course following an appendectomy under local anesthesia.

SUMMARY.—In 30 patients with preoperative decompensation there were 5 deaths, 1 of which was entirely due to cardiac disease and in 2 cardiac disease played an important rôle. Four days after operation cardiac failure caused the death of a patient who had received a spinal anesthetic. Two patients died several weeks postoperatively of combined

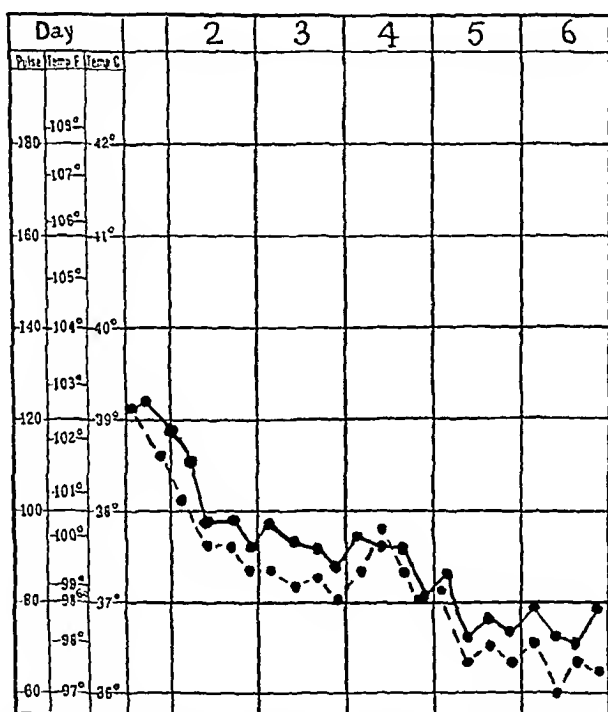


Chart 3.—Record of the postoperative course of a patient with extreme decompensation. The solid line indicates the temperature; the broken line, the pulse rate.

cardiac failure and extensive metastasis of carcinoma, 1 having pneumonia also. A major operation under spinal anesthesia was followed by death from pulmonary embolism during an apparently uneventful recovery.

#### CONGENITAL HEART DISEASE

Death or signs of collapse, particularly with ethyl chloride, chloroform or ether anesthesia, are not infrequently reported in cases with associated congenital heart disease.<sup>11</sup> Lidwill<sup>9</sup> stated that congenital heart disease offers practically no contraindication in the majority of cases. However, he reported a death from cardiac disease following

ethyl chloride and ether anesthesia. Harvey<sup>4</sup> stated that the patient with congenital cardiac disease is ill suited in infancy for the imposition of sudden additional strain, and any operative procedures must therefore be carefully adjusted to the seriousness of the lesion and the degree to which it is compensated.

This series of patients with congenital heart lesion includes 10. There were no deaths. One patient had tachycardia for several days after receiving ether anesthesia for a tonsillectomy and adenoidectomy. Of the 10 patients, 6 were females and 4 males. There were 9 minor operations with ether anesthesia and 1 major operation with ethylene-oxygen plus ether anesthesia. The patients ranged in age from 20 months to 13 years, the average age being 5½ years.

SUMMARY.—With no deaths and but 1 instance of a cardiac complication during recovery in a series of 10 patients with congenital heart disease, it appears that surgical intervention is not to be feared for this group.

#### CORONARY OCCLUSION AND ANGINA PECTORIS

Coronary occlusion markedly increases the surgical risk. Butler, Feeney and Levine<sup>6</sup> found their greatest mortality (44.5 per cent) in patients with this condition. However, among persons for whom the correct diagnosis had been made and proper treatment instituted, their mortality was only 14.3 per cent. Patients for whom the diagnosis had not been made had a mortality of 75 per cent. Proper preoperative diagnosis is of great importance both from the standpoint of adequate treatment and to avoid surgical procedures during attacks of coronary thrombosis. Herrmann and Herrmann<sup>12</sup> stated that patients with coronary occlusion may be subjected to surgical treatment if they are carefully prepared but that the risk is always great.

Among this series of patients there were 8 with coronary occlusion. Two of these had more than 1 operation, there being 10 major and 3 minor procedures. The average age was 49 years, with a maximum of 67 and a minimum of 40. There were 3 females and 5 males. One death occurred, giving a mortality of 12.5 per cent. The types of anesthesia used were: ethylene-oxygen, in 6 cases; local, in 5, and spinal and ethylene-oxygen plus ether, in 1 each. Phelps<sup>16</sup> advised against the prolonged administration of nitrous oxide and oxygen in these cases.

The death occurred after 5 operations on a man of 45, who had coronary occlusion and multiple emboli. Two of the operations performed were embolectomies, and 3 were amputations. Local, ethylene-oxygen and ethylene-oxygen plus ether were types of anesthesia used.

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16. Phelps, A. E.: Coronary Disease in Surgical Patients, *Ann. Surg.* **87**:32 (Jan.) 1928.

In addition to this case, there were 4 others with poor postoperative recovery. All the complications were cardiac. One patient had transient tachycardia, and 2 had attacks of coronary thrombosis. These 3 patients had received ethylene-oxygen anesthesia. In the fourth patient, who had auricular fibrillation preoperatively myocardial failure developed after a suprapubic cystotomy under local anesthesia.

**SUMMARY.**—Since 1 of 8 patients with coronary occlusion died of cardiac disease, the mortality rate of 12.5 per cent apparently indicates that anesthesia and surgical operations have a graver risk in this type of cardiac disease than in the types previously mentioned.

Patients with angina pectoris are also poor risks. Butler, Feeney and Levine reported a mortality of 7.7 per cent in 41 operations on 35 patients. They found danger of coronary thrombosis in these patients. Sprague<sup>5</sup> reported 4 deaths in a series of 13 cases. There were only 3 patients suffering from angina pectoris in the present series, and of these 1 died (a mortality of 33.3 per cent), while 1 had a poor recovery. A man of 62 with a blood pressure of 220 systolic and 110 diastolic and frequent anginal attacks had a suprapubic prostatectomy under ethylene-oxygen anesthesia. For ten days he had a low grade fever. On the eleventh day he had a fainting attack accompanied by precordial pain. He recovered and was discharged from the hospital, but his activity was greatly restricted.

The death in this group was that of a patient who had a rectal polyp excised under local anesthesia. Two and one-half hours after the operation he died suddenly from what appeared clinically to be coronary thrombosis. Unfortunately, autopsy was not permitted in this case.

**SUMMARY.**—One postoperative death from cardiac disease in 3 cases of angina pectoris indicates a grave risk when one contemplates anesthesia or surgical intervention in the presence of this type of cardiac disease.

#### HEART BLOCK

Herrmann and Herrmann<sup>12</sup> stated that heart block and bundle branch block are very severe conditions which predispose to ventricular cessation during surgical procedures. They urged that only the most necessary operations be attempted on these patients. Lidwill<sup>9</sup> expressed the belief that patients with heart block may withstand operation well, provided there is no decompensation and no Adams-Stokes syndrome. Blackford<sup>13</sup> and his collaborators reported on 7 patients with partial or complete heart block who were operated on with no deaths.

In this series there were only 4 cases of heart block. Three of the patients were men and 1 was a woman. The maximum age was 78 and the minimum 25. There were 3 major operations and 1 minor operation.

Local anesthesia was employed in 3 of these cases, while in 1, in which a radical mastoidectomy was performed, ethylene-oxygen plus ether anesthesia was used. All the patients survived the operation, and all had uneventful recoveries. One man, 78 years old, who had a partial orchidectomy with local anesthesia had had a suprapubic prostatectomy with ethylene-oxygen anesthesia four years previously. At the time of the first operation heart block was present.

SUMMARY.—The 4 cases of heart block with no deaths or postoperative complications suggest that this type of cardiac disease does not contraindicate anesthesia or operation.

#### ACUTE PERICARDITIS

Among the patients in this series there was only 1 with acute pericarditis. This was a child of 3 years who entered the hospital acutely ill. She had decompensation for two weeks before admission and had been in an oxygen tent almost constantly. Five operations were performed: incision and drainage for acute osteomyelitis of the shoulders and thighs, a myringotomy, 2 incisions and drainage of mediastinal abscesses and a pericardotomy. She died of pyopericardium and septicemia. Ether and local anesthetics were employed during the various operations.

#### MISCELLANEOUS CARDIAC LESIONS

Miscellaneous cardiac lesions include questionable rheumatic heart disease, cardiac murmurs, bradycardia and all lesions not clearly diagnosed. There were 31 patients with such lesions in this series, with 2 deaths, or a mortality of 6.4 per cent. There were 12 males and 19 females, with an average age of 35, a maximum of 71 and a minimum of 4 years. Seventeen major and 14 minor operations were performed. The types of anesthesia used were: ethylene-oxygen, in 6 cases; local, in 10; ether, in 7; ethylene-oxygen plus ether, in 4; nitrous oxide-oxygen, in 3 (minor operations), and spinal, in 1.

The 2 deaths were unrelated to the cardiac or pulmonary systems. One occurred seven days postoperatively (local anesthesia) from respiratory failure in a patient with a pineal tumor. The other death was caused by streptococcic septicemia and followed a radical mastectomy under ethylene-oxygen anesthesia. There were 5 other postoperative complications, none of them cardiac or respiratory. Two of the complications with recovery were hemorrhage after tonsillectomy.

#### COMMENT

In the 170 cases reported by Sprague,<sup>5</sup> 5 of the patients died on the operating table. There were no deaths on the operating table in the present cases.

There were 4 deaths during the first four postoperative days. One male died suddenly of apparent coronary thrombosis two and one-half hours after the removal of a rectal polyp under local anesthesia. One patient died of hemorrhage on the day of operation following a thyroidectomy. Another patient died on the second day after thyroidectomy of an "asthenic reaction to thyroidectomy." One patient died on the fourth postoperative day of cardiac failure. All the other deaths occurred later, some as late as from five to six weeks after operation.

Following 336 operations, considering the patients with each type of cardiac disease separately, the mortality rates were as follows: for patients with angina pectoris, 33.3 per cent; for patients with arteriosclerotic heart disease, 16.6 per cent; for patients with decompensation, 13.3 per cent; for patients with coronary occlusion, 12.5 per cent, and for patients with hypertensive heart disease, 10.9 per cent. The patients with other types of cardiac disease had a lower death rate (table 5).

TABLE 5.—*Mortality Rate Following Three Hundred and Thirty-Six Operations*

Preoperative Diagnosis	Total Death Rate, Percentage	Death Rate for Cardiac Disease, Percentage
Angina pectoris.....	33.3	33.3
Arteriosclerotic heart disease.....	16.6	0
Decompensation.....	13.3	3.3
Coronary occlusion.....	12.5	12.5
Hypertensive heart disease.....	10.9	3.2
Compensated myocarditis.....	9.0	0
Thyrotoxic heart disease.....	8.3	2.7
Miscellaneous heart disease.....	6.4	0
Compensated valvular heart disease.....	1.6	0
Heart block.....	0	0
Congenital heart disease.....	0	0

In considering the patients who died postoperatively of cardiac disease, it is seen that 33 per cent died of angina pectoris, 12 per cent of coronary occlusion, 3.3 per cent of decompensation, 3.2 per cent of hypertensive heart disease and 2.7 per cent of thyrotoxic heart disease.

In this series there were 27 patients who recovered but who suffered from postoperative cardiac complications (table 4). These complications were as follows: fibrillation, 12 cases; fibrillation and associated thyroid crises, in 8; coronary thrombosis on the second postoperative day, in 2; anginal attack on the fifth postoperative day, in 1; anginal attack on the eleventh postoperative day, in 1; symptoms of myocardial insufficiency, in 1, and tachycardia for several days after operation, in 1.

It is of interest to note that in 1 patient who had had an uneventful recovery following a previous operation under local anesthesia not included in this series, fibrillation developed following ethylene-oxygen anesthesia with moderate lack of oxygen and straining respiration. Two patients had an uneventful course after ethylene-oxygen anes-

thetia for major operations; in each instance when ether was added to the ethylene and oxygen as a second anesthetic, fibrillation occurred.

Two postoperative cardiac complications followed nitrous oxide-oxygen anesthesia. An elderly woman had an anginal attack following a retrogasserian neurectomy performed with the patient in the sitting position, and a man of 34 years had fibrillation for four days following a bone graft to the lower extremity.

It has been found by clinical observation<sup>15</sup> that the diseased heart cannot tolerate lack of oxygen or asphyxia. Since lack of oxygen is frequently associated with nitrous oxide-oxygen anesthesia,<sup>17</sup> the results just mentioned are not surprising. Nitrous oxide also causes a marked rise in the blood pressure.<sup>18</sup> The importance of avoiding asphyxial strain is also stressed by Hewitt.<sup>11</sup>

The 12 postoperative pulmonary complications with recovery were as follows: pneumonia, in 4 cases; cough, in 4; atelectasis, in 2, and râles of a few days' duration, in 2. With ethylene-oxygen plus ether anesthesia (with a large amount of ether employed) 28.5 per cent of the operations were followed by pulmonary complications. In the cases in which ether anesthesia was used 6.2 per cent of the patients had pulmonary complications, and in the cases in which nitrous oxide-oxygen anesthesia was used 4.3 per cent had pulmonary complications. The use of local or ethylene-oxygen anesthesia resulted in the lowest number of pulmonary complications.

Table 6 shows the relationship of anesthesia to the final cardiac condition.

Three patients among the 23 receiving spinal anesthesia had cardiac complications related to the anesthesia (13 per cent). In the cases in which ethylene-oxygen plus ether anesthesia was used 5.7 per cent of the operations were followed by death due to cardiac disease. Fewer complications occurred postoperatively after the use of local anesthesia, and fewer deaths due to cardiac disease resulted with the use of local or ethylene-oxygen anesthesia.

**SUMMARY.**—It must be emphasized that a high percentage of the operations performed on patients with grave cardiac lesions were operations of necessity, not of selection. A high percentage of the operations were major surgical procedures, many of them very extensive. In view of these facts, it is of interest to note the low percentage of actual deaths from cardiac disease that occurred.

There were only 27 instances (8 per cent) of postoperative cardiac complications with recovery in a series of 336 cases of surgical pro-

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17. Cushny, A. R.: *Textbook of Pharmacology and Therapeutics*, ed. 7, Philadelphia, Lea & Febiger, 1918, p. 228.

18. Gwathmey,<sup>2</sup> p. 30.

cedures on persons with cardiac disease. This suggests that the complications which can be expected are not of sufficiently frequent incidence to warrant the rejection of anesthesia and surgical intervention for patients to whom operation offers improvement in their condition.

Since only 6 deaths due to pulmonary disease and 3 due to cardiac-pulmonary disease occurred in 336 cases, the incidence of death due to pulmonary disease in persons with heart disease is low. Few of the pulmonary complications or deaths were directly related to the cardiac disease.

TABLE 6.—*Relationship of Anesthesia to the Final Cardiac Condition*

Anesthesia	Number of Cases	Deaths Due to Cardiac Disease			Deaths Due to Pulmonary Disease			Deaths Due to Other Causes		Cardiac Complications with Recovery		Pulmonary Complications with Recovery	
		Hospital			Hospital			Hospital		Recovery		Recovery	
		Related	Unrelated	Home	Related	Unrelated	Home	Related	Home	Related	Unrelated	Related	Unrelated
Ethylene-oxygen.....	106	..	1*	..	..	..	..	4	..	11	3†	3	..
Local.....	101	1‡	1§	..	1‡	3	..	4	1	3	1	1	1
Ethylene-oxygen + ether	35	2#	..	..	..	..	..	..	..	3	..	1	..
Ether.....	32	..	1†	..	..	..	..	1	1	2	1	2	..
Spinal.....	23	3	..	1	..	1	..	..	..	1	..	..	..
Nitrous oxide-oxygen...	23**	..	..	..	..	..	..	..	..	1	..	1	..
Local + ethylene-oxygen	10	..	..	1	..	..	..	..	..	1	..	..	..
Ethylene-oxygen + ether	7	..	..	..	..	..	..	..	..	..	..	2	..
Local + nitrous oxide-oxygen.....	2	..	..	..	1	..	..	..	..	1	..	..	..
Sacral.....	2	..	..	..	..	..	..	2	..	..	..	..	..
Spinal + ethylene-oxygen.....	2	..	..	..	..	..	..	..	..	..	..	1	..
Caudal.....	1	..	..	..	..	..	..	1	..	..	..	..	..
Nitrous oxide-oxygen and ethylene-oxygen..	1	..	..	..	..	..	..	..	..	..	..	..	..
Total.....	345	6	3	2	2	4	..	11	2	23	5	11	1

\* Coronary occlusion.

† Angina pectoris and coronary thrombosis.

‡ Thyrotoxic heart disease.

§ Angina pectoris.

# Later.

†† Pericarditis.

|| Embolus.

\*\* Thirteen minors.

## SUMMARY

From the results of this survey the following assumptions may be made:

Since there were only 6 deaths due to cardiac disease and 2 deaths due to pulmonary disease related to the surgical intervention and anesthesia in 336 patients who underwent 345 operations, the resulting mortality of 2 per cent indicates that as a group patients with cardiac disease are fairly good surgical risks.

Angina pectoris, coronary occlusion, decompensation, hypertension and thyrotoxic heart disease are, in the order named, the most serious diseases with which one has to deal.



Contrary to the belief of several authors, inhalation anesthesia, particularly ethylene-oxygen anesthesia, is safe when a high percentage of oxygen is used and asphyxia or struggling is avoided. Ethylene-oxygen and local anesthesia have given the most satisfactory results in this series of cases. The use of spinal, ether or nitrous oxide-oxygen anesthesia has increased the incidence of postoperative complications and death.

Dr. Edmund Andrews assisted in making this study, and Dr. Cornelius Hospers, Dr. Francis Murphy and Dr. William Johnson assisted in reviewing case histories.

# SURGICAL TREATMENT OF CARCINOMA OF THE HEAD OF THE PANCREAS AND OF THE AMPULLA OF VATER

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The ultimate results of radical operation on the pancreas and ampulla of Vater have not been as successful as one would desire because of several factors, the chief of which are: (1) the insidious onset of disease; (2) the poor condition of the patients; (3) the relative inaccessibility of the lesions; (4) the proximity of important structures which cannot be sacrificed, and (5) technical difficulties. Thus there has been a great tendency to treat such lesions in a more conservative manner. This being the case, it seemed of interest to compare the results obtained from the radical procedures with those following purely palliative operations in order to ascertain whether one is justified in attempting complete removal of the diseased tissue.

This study is based on 179 cases, in 158 of which the lesion originated in the head of the pancreas; in the remaining 21 it originated in the ampulla of Vater. The average age of these patients, 70.4 per cent of whom were men, was 56.3 years. The youngest patient was a man of 23 and the oldest a man of 77. Preliminary cholecystostomy was performed in 10 per cent of the cases in order to promote biliary drainage and to improve the general condition of the patient before attempting a more radical procedure.

Radical resections of the ampulla of Vater have not been numerous. Halsted<sup>1</sup> is credited with having performed the first operation of this nature in February 1898, and his patient lived for nine months. Mayo<sup>2</sup> performed the second resection of the ampulla in January 1901. The cases reported in the literature up to 1927 were carefully reviewed by Cohen and Colp.<sup>3</sup> They found that 59 radical operations had been

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1. Halsted, W. S.: Contributions to the Surgery of the Bile Passages, Especially the Common Bile-Duct, *Bull. Johns Hopkins Hosp.* 11:1 (Jan.) 1900.

2. Mayo, W. J.: Cancer of the Common Bile-Duct: Report of a Case of Carcinoma of the Duodenal End of the Common Duct, with Successful Excision, in *Collected Papers of the Mayo Clinic*, Philadelphia, W. B. Saunders, 1909, vol. 1, p. 365.

3. Cohen, Ira, and Colp, Ralph: Cancer of the Periapillary Region of the Duodenum, *Surg., Gynec. & Obst.* 45:332 (Sept.) 1927.

performed for carcinoma of the periampullar region, transduodenal resection being performed in 53 cases with a mortality of 44 per cent. Since 1927 other surveys have been made by Walters,<sup>4</sup> Potter,<sup>5</sup> Lauwers<sup>6</sup> and Hunt,<sup>7</sup> the last-mentioned finding 17 cases in addition to presenting 1 of his own.

Twenty-one patients with carcinoma of the ampulla of Vater have been submitted to operation at the Mayo Clinic. In 14 cases a purely palliative procedure seemed indicated. Thus, cholecystogastrostomy was performed twelve times and cholecystoduodenostomy and choledochoduodenostomy once each. Four of the patients did not recover from the operation, but the average postoperative life of those who did was thirteen and nine-tenths months. In the 7 remaining cases in this group the lesion appeared to be amenable to complete extirpation. Consequently, resection of the ampulla of Vater together with the tumor was carried out (table 1).

Four of the 5 patients who survived the operation were completely relieved of their symptoms and lived for one year and three months, two

TABLE 1.—*Radical Operations for Carcinoma of the Ampulla of Vater*

Operation	Cases
Resection, transduodenal .....	2
Resection, transduodenal, and choledochotomy .....	2
Resection, transduodenal, and choledochoduodenostomy .....	1
Resection, transduodenal, choledochoduodenostomy and cholecystostomy.....	1
Resection, transduodenal, and cholecystoduodenostomy .....	1
Total.....	7

years and two months, two years and two months and three years, respectively. One patient was not traced. When an attempt was made to compare these results with those obtained following palliative operations, it was found that the average postoperative life of the patients in the former group was one year longer. On the other hand, however, palliative procedures did not entail as great an operative risk, and in addition 1 of the patients lived two years, free from symptoms until just before the end. Since it was difficult to arrive at definite conclusions while one was dealing with groups composed of so few cases, it was deemed advantageous for the sake of comparison to select a large series of cases of conditions closely related to malignant lesions of the ampulla

4. Walters, Waltman: Resection of the Common and Hepatic Bile Ducts and Ampulla of Vater for Obstructive Lesions, *Surg., Gynec. & Obst.* **56**:235 (Feb.) 1933.

5. Potter, E. B.: Successful Resection of Common Biliary Duct for Carcinoma of Ampulla of Vater, *Ann. Surg.* **98**:369 (Sept.) 1933.

6. Lauwers, E.: Traitement chirurgical du cancer vaterien, *J. de chir.* **42**:833 (Dec.) 1933.

7. Hunt, Vern: Personal communication to the authors.

of Vater. Therefore carcinoma of the head of the pancreas, which seemed to fulfil the necessary qualifications, was utilized for this purpose and was made the object of a second study.

Complete removal of neoplasms of the pancreas has been attended with very little success. Few indeed are the cases in which a prolonged survival has been obtained, in spite of the encouraging report of Gordon-Taylor,<sup>8</sup> whose patient has now lived seven years after such an operation. Thus, carcinoma of the head of the pancreas is usually treated by palliative measures similar to those employed for lesions of the ampulla of Vater. Studies of these conservative procedures have been reported by Gorman,<sup>9</sup> Clute,<sup>10</sup> Walters and McVicar,<sup>11</sup> Judd and Parker<sup>12</sup> and Collier and Winfield.<sup>13</sup>

Some form of anastomosis between the biliary tract and the intestines was performed in 158 cases of lesions involving the head of the pancreas. Because of the difficulty encountered in making a definite diagnosis of carcinoma in some instances, this series was divided into two groups and each was studied separately. The first group is composed of 94 cases in which the diagnosis of malignant growth was verified at the time of operation, at subsequent postmortem examination or later by the referring physician. In 64 cases the differentiation of carcinoma and chronic pancreatitis could not be made with certainty, although in the opinion of the surgeon a malignant condition was the more likely in the majority of cases (table 2).

Since the immediate factor which endangers the life of these patients is obstruction of the biliary tract some form of anastomosis between the biliary tract and the intestines is the operation of choice, for it provides prolonged drainage of the biliary system without the loss of bile. The two methods most frequently employed are cholecystogastrostomy and cholecystoduodenostomy. The choice of one or the other of the two procedures was determined solely by the ease with which the stomach or the duodenum could be approximated to the gallbladder. Other portions of the intestines were utilized for the anastomosis only

8. Gordon-Taylor, G.: The Radical Surgery of Cancer of the Pancreas, *Ann. Surg.* **100**:206 (July) 1934.

9. Gorman, J. J.: Adenocarcinoma of Head of Pancreas, *Southwestern Med.* **16**:259 (June) 1932.

10. Clute, H. M.: Choledochoduodenostomy in Cancer of Pancreas, *S. Clin. North America* **13**:617 (June) 1933.

11. Walters, Waltman, and McVicar, C. S.: Relief of Obstructive Jaundice from Tumors in the Head of the Pancreas, *Ann. Surg.* **89**:237 (Feb.) 1929.

12. Judd, E. S., and Parker, B. R.: Biliary Intestinal Anastomosis for Obstructive Jaundice: Analysis of One Hundred and Thirty-Seven Consecutive Cases, *Arch. Surg.* **17**:1 (July) 1928.

13. Collier, F. A., and Winfield, J. M., Jr.: Evaluation of Palliative Operation for Cancer of the Pancreas, *Am. J. Surg.* **25**:64 (July) 1934.

when the stomach and duodenum were not readily available. In one case previous cholecystectomy necessitated some other form of union, and thus choledochoduodenostomy was performed.

Patients suffering from obstructive jaundice always present a poor surgical risk, and this is especially true, in spite of the best of preoperative care, when the lesion involves the head of the pancreas. The three main complications to be feared in this type of case are hemorrhage, hepatic insufficiency and renal insufficiency. The best method of protecting the patient against hemorrhage during and after operation is to give one or more transfusions of whole blood before and after operation. Calcium chloride also has been used intravenously to increase the coagulability of the blood, but just what part it plays is not clearly understood. Since an injured liver can utilize carbohydrates more readily than other nutrient substances, large quantities of 10 per cent solution of dextrose are administered intravenously, either alone or combined

TABLE 2.—*Palliative Operations for Carcinoma of the Head of the Pancreas*

Type of Operation	Diagnosis Verified	Diagnosis Questionable	Total
Cholecystogastrostomy.....	66	56	122
Cholecystoduodenostomy.....	15	6	21
Cholecystojejunostomy.....	7	2	9
Cholecystocolostomy.....	4	0	4
Choledochoduodenostomy.....	1	0	1
Reconstructive cholecystogastrostomy*.....	1	0	1
Total.....	94	64	158

\* Cholecystogastrostomy performed elsewhere previously.

with 1 per cent solution of sodium chloride or 2 per cent solution of racemic sodium lactate. The rôle of racemic sodium lactate is not definitely known, but it seems to aid in restoring hepatic function in some instances. These measures are further supplemented by prescribing a diet high in carbohydrates. The increased intake of fluid just described serves a double purpose in the presence of jaundice, for it is an excellent treatment for a coexisting toxic nephrosis.

The mortality at the hospital for this series of palliative operations was high. The patients who survived the operation, however, were relieved of their most troublesome symptoms, pain, jaundice, pruritus and episodes of chills and fever, except in a very few instances. The patients who derived no benefit from the operation comprised but 4 per cent of those who survived. These patients were the ones in whom the carcinoma was farthest advanced at the time of operation, and most of them died within three months after the procedure. Obstruction of the pancreatic duct is often one of the terminal complications in these cases.

The average length of life after leaving the hospital for the patients with verified carcinoma of the head of the pancreas was ten and two-tenths months. The patients in whom carcinoma of the head of the pancreas and chronic pancreatitis could not definitely be distinguished lived, on an average, eleven and nine-tenths months. It would appear that the discrepancy between these figures could be accounted for by the inclusion in the latter group of several patients with simple pancreatitis. Furthermore, the fact that some patients with a questionable diagnosis did survive from three to six and a half years lends considerable weight to this opinion. Nevertheless, the number of incorrect diagnoses in a large series of cases is relatively few, for the surgeon can form a rather accurate opinion of the condition with which he is dealing but is restrained from offering a dogmatic statement because a specimen for biopsy was not taken.

#### COMMENT

Although the results following operation for carcinoma of the ampulla of Vater or for carcinoma of the head of the pancreas leave much to be desired, there is still something to be said in favor of such operations. In spite of the improvement in the methods of diagnosing disease of the biliary tract, in an occasional case there are typical features of carcinoma of the lower end of the common duct in which obstructive jaundice is found to be the result of a calculus. In other cases in which pathologic changes are found in the head of the pancreas it may be difficult to determine the true nature of the condition. If the lesion subsequently proves to be chronic pancreatitis, anastomosis between the biliary tract and the intestines not only provides the best form of treatment, namely, biliary drainage, but is compatible with life when the patient recovers from the disease. These two factors alone justify operation in such cases.

From the foregoing discussion it appears that palliative operations are justifiable; the data presented in this paper also show, however, that the patients with carcinoma of the ampulla of Vater who survive operation live longer following removal of the growth than those who submit to purely palliative treatment for either carcinoma of the ampulla of Vater or carcinoma of the head of the pancreas. It is known that there will eventually be a fatal result in all cases in which an attempt is not made to resect the neoplasm. Thus, although the surgical risk is greater, radical measures offer the only prospect of cure. Even when the outcome is not all what had been anticipated and the growth recurs, the person still may enjoy a longer period of useful life. There are not many surgical procedures now employed successfully that have not undergone the same metamorphosis. Every attempt adds much to the knowledge concerning the disease, and some day a complete cure will

be accomplished. Of course, this is an extremely small series from which to draw definite conclusions, but from the information available at present, radical operations appear to be justified in certain selected cases of carcinoma of the ampulla of Vater in which there is a reasonable chance of procuring a successful result.

#### SUMMARY

A study was made of 179 patients submitted to surgical intervention for lesions originating either in the head of the pancreas or in the ampulla of Vater. The former was found to be the primary site 158 times; the latter, 21 times.

Carcinoma of the head of the pancreas may be difficult to distinguish from chronic pancreatitis. In cases in which the diagnosis of malignant growth was verified following palliative operations, the patients enjoyed an average of ten and two-tenths months of useful life after leaving the hospital. In the questionable cases in which the same procedures were performed, the patients enjoyed an average life of eleven and nine-tenths months. Only 4 per cent of those who survived obtained no benefit from the operation.

Five of the 7 patients who were subjected to transduodenal resection of the ampulla of Vater for carcinoma recovered, and their average postoperative length of life was twenty-five and eight-tenths months. The patients in this group who survived some form of anastomosis between the biliary tract and the intestines lived, on an average, thirteen and nine-tenths months.

Radical resection of carcinoma of the ampulla of Vater sustains life for a longer period than more conservative treatment, and it offers the only prospect there is of cure.

# URINARY CALCULI IN BONE DISEASES

REVIEW OF THE LITERATURE AND REPORT OF CASES

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A review of the literature reveals only an occasional reference to a report of the occurrence of urinary calculi in association with various bone diseases. However, within recent years an increased interest has been manifested in the relation of urinary lithiasis to bone diseases. The World War offered an opportunity to study the effect of suppurative bone lesions (Paul, W. Weber, E. Joseph) and gunshot wounds of the vertebral column (Benda) on calculus formation in the kidneys. W. Weber has recently reported 9 cases and Barr and Charles 7 cases of urinary calculi in association with various bone diseases, i. e., osteomyelitis, vertebral fractures, arthritis, coxitis, tuberculosis of the spine, rickets, fractures, etc.

With the exception of the article by Barr and Charles, the American contributions to the subject of urinary calculi in cases of bone diseases are limited to reports of single cases by various writers, including O'Connor, Harper, Herman, Borman and others, and to general statements on the subject by Eisenstaedt, Squier and Keyser. In a discussion of the etiologic factors concerned in the production of urinary calculi, Eisenstaedt emphasized the rôle of prolonged immobilization for fractures and wounds, especially chronic suppurating lesions involving the bones, and subsequent infection of the urinary tract with *Bacillus coli* or staphylococci. He also noted the occurrence of urinary calculi following fractures of the spine and stated that the spinal diseases commonly associated with urinary calculi are spondylitis, arthritis deformans and spondylitis deformans. In a comprehensive discussion of the etiologic factors in nephrolithiasis, Squier stressed the rôle of calcium metabolism in the genesis of nephrolithiasis and emphasized the importance of considering the relation of disturbances of calcium metabolism to stone formation in various bone diseases, i. e., osteoporosis, osteomalacia, osteitis deformans, osteopsathyrosis, chronic septic coxitis and severe rickets. He also mentioned the occurrence of renal calculi following traumatic injuries and diseases of the spinal cord and



compound fractures of long bones in which the healing process has been prolonged.

While it has long been known to the pathologist that calcareous deposits are found in the kidneys and other organs in severe rickets, osteo-arthropathies, bone injuries and tumor metastases, no particular mention is made of the occurrence of renal calculi in these conditions. These so-called calcium deposits or metastases are found in various organs of the body, the kidney being usually the first to be involved and then, in the order of relative frequency, the heart, lungs, stomach and skeletal musculature.

The decided paucity of reports of the association of urinary lithiasis with various bone diseases may be attributed to the fact that frequently it is impossible to establish an etiologic relationship between the urinary calculi and the bone disease inasmuch as the symptoms produced by such calcareous concretions usually occur long after the arrest of the original bone lesion, or the calculi are symptomless and the diagnosis is made only at autopsy. Often their occurrence may be overlooked or not recognized, as attention is directed wholly to the major bone lesion.

It is our purpose in this paper to review the contributions to the subject of urinary lithiasis in bone diseases and to present 14 cases. Four cases occurred following amputation of extremities, 2 following osteomyelitis, 4 following a fracture of the femur or of the pelvis, 1 following tuberculosis of the hips, 1 following arthritis deformans with an associated osteitis deformans and 2 in association with scoliosis. We have also observed 6 cases of urinary lithiasis associated with osteitis deformans, which have been reported elsewhere.

#### BONE SUPPURATION

Although the relation of focal and systemic infections to the formation of renal calculi has been the subject of much investigation in recent years, little consideration has been given to bone suppuration as a possible etiologic factor. The earliest recorded case of urinary calculus associated with suppurative bone disease was that reported by Adams in 1850: A boy was treated for an infection of the knee joint at the age of 12, and several months later osteomyelitis of the os pubis developed.

The recent reports of Paul, W. Weber, Lepoutre and others in this connection are of extreme importance and have served to establish a definite etiologic relationship between bone suppuration and nephrolithiasis. Paul reported 20 cases of nephrolithiasis in wounded war veterans. There was a definite history of bone suppuration with the associated systemic infection that accompanies osteomyelitis in every case with the exception of one in which a soldier had sustained multiple

shrapnel wounds of the right thigh and buttock. In the discussion of Paul's paper, Herman reported a case of renal and ureteral calculi in an 8 year old boy. The condition was primarily osteomyelitis of the tibia due to *Staphylococcus aureus*. W. Weber recently reported 3 interesting cases of nephrolithiasis following infections of the bones. The first patient had both legs amputated because of a gunshot wound of the thighs, and osteomyelitis of the stumps developed; the second had a gunshot wound of the pelvis and hip, and in the third osteomyelitis developed following an operation for genu valgum. Lepoutre reported a case of nephrolithiasis following severe war wounds necessitating amputation of the left thigh.

Grossman reported a case of lithiasis following osteomyelitis of the os calcis, clavicle and femur in a 9 year old girl. Borman recently described a case of bilateral renal and ureteral calculi in a 9 year old boy who had osteomyelitis of the left femur. Le Fur cited a case of bilateral renal lithiasis in a young man, aged 20, following an injury of the bone marrow by a bullet. Luys reported the case of a World War veteran, immobilized for an extremely long time because of serious lesions of the spinal marrow and the bodies of the vertebrae, who spontaneously voided several phosphatic vesical calculi. Barr and Charles reported 3 instances of renal calculi occurring in relation to various suppurative bone diseases: 1 in association with osteomyelitis of the right knee, left tibia, left arm and right femur in a 16 year old boy; 1 following multiple comminuted fractures of the left tibia, right metatarsal bones and right ulna and radius, complicated by osteomyelitis at the site of each fracture in a 27 year old man, and 1 following chronic otitis media with suppurative mastoiditis in a 35 year old man.

E. Joseph stated that in his experience many examinations had been made of wounded veterans in whom calculi had developed. Most of these veterans had undergone amputations of an arm or a leg, presumably for infection following bone injuries. He mentioned a case of bilateral lithiasis in a man who had bilateral amputation of the legs. He believed that the great metabolic changes brought about by the amputation in this case were the cause of the lithiasis.

In 1931 Wolf reported his observations on the formation of urinary calculi in patients who had had an amputation of a leg as a result of a war injury. Among 419 patients who had undergone an amputation above the knee joint, 4 later presented renal calculi. Among 300 patients in whom the injured leg was amputated below the knee, 1 acquired renal calculi. The author cited the fact that rats subjected to some sort of mechanical jolting at intervals for three months show hemorrhages in the urinary passages not uncommonly leading to stone formation. He believed that patients who have lost a leg, especially if the artificial leg

is too short, as it very frequently is, suffer a jolting whenever they walk and that this constant unnatural jarring of the body leads ultimately to renal stones laid down on a nucleus of fibrin.

C. K. Smith recently made a study of urinary calculi in children and noted the occurrence of multiple bilateral renal calculi in a girl of 11 years suffering from a diffuse osteomyelitis involving the lower part of the legs, the left thigh and the pelvic bones in the left sacro-iliac region. Nove-Josserand is quoted by Rafin as having recorded a case in which a renal stone was discovered on examination of the roentgenogram and recovered at operation from a child who first had a mouth infection followed by bronchopneumonia and later by grave osteomyelitis.

Lepoutre is of the opinion that there is a definite relation between osseous and osteo-articular involvements and lithiasis and has emphasized the rôle of long immobilization for such diseases in the production of lithiasis. He believes that arthritis may be a factor when the calculi are formed of urates but not when the calculi are composed of phosphates and carbonates. Calculi of the latter type are attributed to a diathesis in which there are disorders in the mobilization of minerals; some of these minerals may be deposited in the urinary passages. He called attention to the fact that the urine of patients in whom calculi develop following prolonged immobilization for bone diseases is usually alkaline, which is favorable to the formation of calculi composed of phosphates or carbonates.

W. Weber stressed the rôle of infection in the formation of urinary calculi in osteomyelitis. He stated that urinary calculi are frequently observed in those bone diseases in which an infection supervenes whether in an exogenous manner, as in complicated fractures and osteomyelitis, or in an endogenous manner, as in chronic infectious arthritis of the spinal column or in infectious arthritis of the hip, especially the bilateral form of the latter lesion.

We have observed urinary lithiasis following amputation of an extremity in 4 cases and following osteomyelitis in 2 cases.

CASE 1.—A. P., a man 58 years old, a jeweler, was admitted to Sinai Hospital on May 20, 1924, with the complaint of difficult urination. The family history was negative. His general health was good until fifteen years prior to this when he underwent an amputation of the right leg below the knee for gangrene.

*Present Illness.*—A year prior to hospitalization the patient began to complain of frequency of urination, nocturia, dysuria, urgency, pollakiuria and incomplete emptying of the bladder. The symptoms had increased in severity for the past three months. The patient had hematuria for the first three months before examination but subsequently on several occasions noticed clots of blood in his urine. He had had pain in his flanks and the lower part of the back off and on for the past year.

*Physical Examination.*—Abnormalities of interest were found on examination of the extremities and the prostate. The amputation stump of the right leg was

healed, and a pulsation was palpable in the popliteal space. Rectal examination disclosed enlargement of the prostate of the second degree; the surface presented no areas of stony hardness.

*Urinalysis.*—The test for albumin was positive, and microscopically the voided urine showed many pus and red blood cells, several epithelial cells and an occasional hyaline and granular cast.

*Course.*—On May 20 cystoscopy was performed under caudal anesthesia. Two calculi, each about the size of a walnut, were seen on the posterior wall of the bladder. There was a marked intravesical bulging of the prostate posteriorly in the form of a median lobe. On May 21 the patient was taken to the operating room, and preparation was made for performing a suprapubic cystostomy. Nitrous oxide and oxygen were administered, but the cardiac and respiratory conditions of the patient were not entirely satisfactory during the anesthesia. A soft rubber catheter was passed into the bladder and 100 cc. of air was injected through it. The usual midline incision was made; the dissection was carried down to the surface of the bladder. Another 100 cc. of air was injected into the bladder and immediately after this the patient stopped breathing, seven minutes having elapsed since the start of the anesthesia. Attempts to revive the patient were unsuccessful. The patient's sudden death was apparently due to an air embolus.

A postmortem suprapubic cystostomy was carried out in order to establish a correct diagnosis. Eighteen calculi, each the size of a small marble, were removed from the bladder. The prostate and a portion of the bladder were also removed. Further examination of the bladder disclosed marked thickening of the walls. Over the entire surface of the organ were seen many ulcerations varying in diameter from 5 to 7 mm. and grayish or greenish gray. The prostate was moderately enlarged, producing an intravesical bulging of the median and lateral lobes. The prostate was firm in consistency and on cross-section offered a gritty and rubbery resistance. Microscopic examination of several sections taken from different portions of the prostate disclosed an infiltrating carcinoma.

*Diagnosis.*—The diagnosis was (1) calculi in the urinary bladder, (2) carcinoma of the prostate, (3) ulcers and gangrene of the bladder, (4) thrombo-angiitis obliterans (left leg) and (5) amputation of the right leg for gangrene.

*CASE 2.*—M. H., a white man 63 years old, a tinsmith, was admitted to Sinai Hospital on Sept. 9, 1932 with the complaint of frequent and painful urination. The family history was without significance. The patient had enjoyed good health until eleven years prior to hospitalization, when he slipped and fell from the roof of a two story building on which he was working. His right arm was mangled, and an immediate amputation at the shoulder joint was necessary. The wound was slow in healing owing to suppuration. The patient stated that he also sustained an injury to his head at the same time, presumably a fracture of the skull, which required operative treatment.

*Present Illness.*—His urinary difficulties began one year after this accident. He began to complain of diurnal frequency, nocturia, hesitancy, urgency, dysuria and weak stream. Four months prior to examination his urinary symptoms appeared to be aggravated. He suffered with pain and burning during the entire act of urination and had difficulty in starting his stream. There was no history of acute retention, hematuria or passing of calculi.

*Physical Examination.*—The findings of interest are recorded here. There was a linear scar, 15 cm. long, extending from the right occipital to the left parietal region. About midway along the scar there was a circular depressed area, 1.5 cm. in diameter. The right arm had been amputated at the shoulder joint. Abdominal

examination disclosed slight tenderness in the left upper quadrant over the kidney and in the left lower quadrant along the course of the ureter. Rectal examination revealed a small flat prostate of a soft and elastic consistency.

*Laboratory Studies.*—A voided specimen of urine showed a definite trace of albumin, and on microscopic examination many pus cells and an occasional red blood cell and hyaline cast were seen. During his stay in the hospital, his blood urea ranged between 30 and 40 mg. per hundred cubic centimeters. The Wassermann reaction of the blood was negative.

*Course.*—Cystoscopic examination was performed on Aug. 12, 1932 in the outpatient department. The capacity of the bladder was 250 cc., and the residual urine was 150 cc. Inspection of the bladder revealed six calculi of varying sizes lying close together. The walls of the bladder were congested and showed many cellules and trabeculations. A roentgenogram showed six calculi in the bladder, two large calculi in the left kidney and a calculus in the right kidney,



Fig. 1 (case 2).—Roentgenogram showing multiple calculi in the bladder, two large calculi in the left kidney and a calculus in the right kidney.

two large shadows in the region of the left kidney and two small shadows in the region of the right kidney (fig. 1).

On September 9, under caudal anesthesia, a bilateral ligation and partial resection of the vas deferens was done. On September 13, under spinal anesthesia, a suprapubic lithotomy was done and the six calculi were removed. The walls of the bladder were thickened and presented numerous cellules and trabeculations. The vesical orifice showed a median bar of moderate size with no enlargement of the lateral lobe. The patient made an uneventful recovery and was discharged from the hospital on November 3.

*Diagnosis.*—The diagnosis was (1) bilateral nephrolithiasis, (2) median bar formation, (3) calculi in the urinary bladder and (4) amputation of the right arm at the shoulder.

**CASE 3.**—M. S., a white man 63 years old, retired, was admitted to Sinai Hospital on May 25, 1934, complaining of hematuria. The family history was

unimportant. In 1902 he sustained a compound fracture of both bones of the right leg, which was followed by gangrene and necessitated amputation below the knee. He had been wearing an artificial leg for twenty years. Three years prior to examination a prostatic punch operation was performed for a median bar.

*Present Illness.*—Four years prior to examination he observed blood in his urine and experienced dull nonradiating pain in his left lumbar region, which recurred at frequent intervals. These attacks were occasionally accompanied by nausea, vomiting, chills and fever. Following the prostatic punch operation, he had diurnal frequency, nocturia, hesitancy and urgency.

*Physical Examination.*—The positive findings were tenderness in the left upper quadrant of the abdomen and left lumbar region. A well healed stump was present in the midportion of the right leg.



Fig. 2 (case 3).—Roentgenogram showing a calculus of the large staghorn type in the left kidney.

*Laboratory Studies.*—Voided urine showed albumin and contained many pus cells and an occasional red blood cell. The blood urea was normal. The result of the phenolsulphonphthalein test was 20 per cent for the first hour and 15 per cent for the second.

*Course.*—Cystoscopy and pyelography were performed on May 28 and revealed a calculous pyonephrosis on the left side. The calculus was of the large staghorn type (fig. 2). On June 1, nephrectomy on the left side was performed under ether anesthesia. The patient had an uneventful recovery, except for a low grade infection of the wound, and was discharged from the hospital on August 12.

*Diagnosis.*—The diagnosis was (1) calculous pyonephrosis on the left side and (2) amputation of the right leg.

**CASE 4.**—D. C., a white man 48 years old, a pedler, was admitted to Sinai Hospital on Nov. 15, 1934. He had had the usual diseases of childhood and

adolescence. In 1926 he had an acute gonorrheal urethritis complicated by a urethral stricture. In August 1930 he was in an automobile accident and sustained a compound comminuted fracture of the right tibia and fibula, which became infected, necessitating an amputation of the right leg below the knee. Four months later his first attack of right renal colic developed. In July 1933 a roentgenogram of the genito-urinary tract revealed multiple calculi in both kidneys. In September 1933 the signs and symptoms of a stone in the bladder developed and he was admitted to the hospital for cystoscopic removal of the vesical calculus and transurethral resection of a median bar.

*Present Illness.*—Following the latter treatment the patient enjoyed good health until two months before his final admission to the hospital, when he noticed blood in his urine on several occasions. He also complained of persistent dull pain in both lumbar regions which did not radiate. There were diurnal frequency (every



Fig. 3 (case 4).—Roentgenogram showing multiple calculi in both kidneys.

two hours) and nocturia (from one to three times), but no dysuria, tenesmus or burning. There were no chills, fever, nausea or vomiting. He had noticed a progressive loss of weight, strength and appetite.

*Physical Examination.*—The important positive findings were mitral insufficiency and tenderness in both upper quadrants of the abdomen and in both lumbar regions.

*Laboratory Studies.*—The urine showed a trace of albumin and contained many pus and red blood cells. The blood urea was 65.91 mg. per hundred cubic centimeters, and the Wassermann reaction of the blood was negative.

*Course.*—Cystoscopy performed on Nov. 14, 1934 revealed the presence of pus in both kidneys and marked impairment in the function of each kidney. The phenolsulphonphthalein excretion from the left kidney was 3 per cent and that from the right kidney only 1 per cent in fifteen minutes. A plain roentgenogram of the genito-urinary tract revealed multiple calculi in both kidneys (fig. 3). On November 17 a nephrolithotomy was done under gas and ether anesthesia. Five

stones were removed from the left kidney, which showed advanced pyonephrosis. The patient appeared to be in a state of shock for the next twenty hours, with marked cardiac embarrassment and relative anuria. He responded poorly to the usual supportive measures and died four days after operation.

*Diagnosis.*—The diagnosis was (1) bilateral multiple renal calculi, (2) bilateral pyonephrosis and (3) amputation of the right leg following fracture.

CASE 5.—A. N., a white man 52 years of age, a store keeper, married, gave a history of osteomyelitis at the upper end of the right humerus at the age of 12 necessitating four operations and resulting in marked shortening of the arm. He began to have renal colic on the left side seven years ago and following cystoscopic dilatation passed a small stone. He was seen by us for the first time in June 1932 with the usual symptoms of prostatism. A prostatic resection was performed on June 15. The symptoms of prostatism returned in September 1933, and a second prostatic resection was performed on June 8, 1934. A good functional result was



Fig. 4 (case 6).—Roentgenogram showing bilateral renal calculi. The arrows point to the calculi.

obtained. On October 11 the patient had left renal colic and passed a small stone about the size of a pea. A plain roentgenogram revealed no shadows in the renal or ureteral regions.

*Diagnosis.*—The diagnosis was (1) renal calculus on the left (passed) and (2) osteomyelitis of the right humerus.

CASE 6.—A. J. B., 33 years old, single, white, a physician, had nothing of importance in his past history except an osteomyelitis involving the lower ends of the right radius and ulna at the age of 5 years which necessitated two operations.

*Present Illness.*—On April 3, 1934, a painless hematuria developed which persisted for six days. For a year he had had several attacks of sharp pain in the right upper quadrant of the abdomen and right loin radiating downward anteriorly to the right groin. A voided specimen of urine showed from 15 to 20 red blood cells and an occasional pus cell. The results of the physical examination were negative.



*Course.*—Cystoscopy and pyelography performed on April 10 revealed two small calculi in the left kidney and one in the midportion of the right kidney. Following dilatation of the ureters the patient passed three small stones which contained mixed phosphates. He was put on an acid ash-producing diet with a high content of vitamin A but failed to adhere to it after the first few weeks. He returned on October 10, complaining of sharp pain in the region of the right kidney accompanied by chills, fever and hematuria. A plain roentgenogram of the genito-urinary tract at this time revealed a right angle calculus in the region of the pelvis of the right kidney and a shadow about the size of the head of a match in the upper pole and a similar shadow in the lower pole of the left kidney (fig. 4). Following conservative treatment the hematuria, chills and fever promptly subsided. The same dietary restrictions have been advised.

*Diagnosis.*—The diagnosis was (1) bilateral renal calculi and (2) osteomyelitis of the right wrist.

#### INJURIES OF VERTEBRAE AND CORD

It is a well known fact that a fracture of the vertebrae with injury to the spinal column may be followed by a rapid formation of renal calculi. The earliest report of such a case in the English literature was contributed by Costello in 1833. Costello stated that Earle in a report made prior to 1833 had described several cases of lithiasis, which he attributed to a subacute inflammatory condition of the kidneys induced by injuries to the lumbar region. In 1837 Ollivier reported a case of renal calculi following a spinal injury. In 1868 Bastian found several calculi in the renal pelvis during an autopsy on a patient who had died from an injury of the spine. In 1875 Lediard cited a case of vesical calculus developing after an injury of the spine. In 1882 H. Smith reported the occurrence of a vesical calculus after an injury of the spine which resulted in a paralysis of the lower half of the body. In 1884 Puzey reported a case of renal calculi following a fracture of the spine. In 1887 Maschka reported 3 cases of renal lithiasis following compression of the spinal cord; 2 were associated with tumors of the vertebral column and 1 followed a fracture of the vertebrae. Benda noted a number of cases of extensive formation of renal calculi in a series of 50 autopsies on soldiers who died of gunshot wounds of the spinal cord.

In the German literature the relation of injuries of the vertebrae and cord to renal lithiasis was first stressed by Bramann in 1891. In 1895 Müller reported the occurrence of bilateral nephrolithiasis in 8 of 10 cases of severe injuries of the spinal column. He explained the occurrence of renal calculi in these cases on the basis of a simultaneously existing injury of the kidney itself. In 1896 Kocher reported a case of vesical calculus in a man with a healed compression fracture of three dorsal vertebrae. In 1897 A. Weber observed a case of bilateral renal calculi in a young man, 19 years old, after a fracture of the vertebrae

resulting from a fall on the back. In 1898 Wagner and Stolper reported a case of nephrolithiasis following a fracture of the fourth thoracic and first lumbar vertebrae accompanied by complete transverse destruction of the cord in a man 35 years old.

In 1895 Müller stated that a study of the literature shows that stone formation in the kidneys occurs in about 10 per cent of the cases of fracture of the vertebrae when this is accompanied by paralytic symptoms. The incidence of stone formation following such injuries appears to be greater in males. The length of time required for the formation of renal calculi following such injuries is variable, but usually from three to six months elapse before symptoms of renal colic are manifested. Frequently in these cases the presence of urinary calculi is unsuspected and the diagnosis is made from roentgenographic findings during further studies of the bone injury. However, O'Connor reported a case of renal and vesical calculi confirmed by a roentgenogram taken four weeks after the primary injury and three weeks after the onset of urinary infection. There was a total absence of any previous history suggesting their presence. In Seefisch's case, the patient began to have renal colic eight weeks after the spinal injury, and the diagnosis of renal calculi was confirmed at that time by a roentgenogram.

Young and Waters reported a case of renal stone formation following a fracture of the first and second cervical vertebrae in a 17 year old patient. The lesion of the cord resulted in paralysis of the bladder with infection of the upper urinary tract. Eisendrath cited a case of a large branched calculus in a kidney with complete loss of function of the affected organ occurring five years after a fracture of the spine. Cahill reported a case of recurrent calculus formation in a young man following a fracture of the lower dorsal region of the spine. This patient had a decompression at the site of the fracture. Urinary retention, infection and bilateral pyelitis developed. Young mentioned the case of a young officer whose spinal cord was severed by a machine gun bullet. Marked urinary infection developed with multiple calculi in the renal pelves, ureters and bladder.

E. Simon reported the case of a man aged 34 years in whom renal calculi developed as a result of an injury to the spinal cord and fracture of the lumbar vertebrae resulting from a fall from a high scaffold. Conwell reported 100 cases of vertebral fractures without injury of the cord among which he observed 8 cases with renal calculi, viz., 5 following fracture of lumbar vertebrae and 3 following fracture of dorsal vertebrae. Harper, Wallenstein and Cumming recently reported several interesting instances of renal lithiasis following fractures of the cervical and lumbar vertebrae. Haumann reported 5 cases of calculous pyonephrosis developing after transverse myelitis which ended fatally

and 1 case following fracture of the thoracic vertebrae with total paralysis of the legs, bladder and rectum. The cases reported by Geldmacher and Meyer are of special interest as the vertebral injury was followed by the so-called myositis ossificans neurotica in addition to the formation of renal calculi. Barr and Charles observed the development of myositis ossificans neurotica and renal calculi in a man 55 years old who had an extensive destructive process of the second and third lumbar vertebrae with sharp angulation associated with secondary hypertrophic changes in the vertebrae. The destructive process in the vertebrae was attributed to a chronic osteomyelitis or tuberculosis which followed a violent injury at the age of 14 when a machine weighing 125 pounds (56.7 Kg.) fell 9 feet (about 3 meters) and struck the middle of his back.

There are many factors concerned in the formation of renal calculi after injuries of the vertebrae and cord. The most important consideration is the condition of the kidney before and after the accident. The existence of a lesion of the upper urinary tract antedating the spinal injury must always be borne in mind and carefully excluded as a causative factor. Confirmatory evidence of the development of a renal lesion in every case of renal lithiasis following a spinal injury is found in the impaired renal function and alterations of the urinary constituents.

In some cases the formation of calculi is dependent on a primary intrinsic lesion of the kidney, i. e., a rupture or tear of the renal parenchyma with extravasation of blood into the renal pelvis which occurs at the time of the injury to the vertebrae and cord. This view has been upheld by Müller, A. Weber and Wagner and Stolper. Casper showed that blood clots and new connective tissue may form in the renal pelvis or in the parenchyma as a result of trauma and serve as a nucleus for stone formation. In these cases the stones are usually of the oxalate or urate variety.

Oehlecker classified traumatic calculi into two groups: (1) the directly posttraumatic calculi (so-called genuine traumatic calculi) associated with a direct injury to the kidney following which small blood coagula, fibrin floccules, clumps of bacteria or products of inflammation act as the centers for the formation of calculi, and (2) the indirectly posttraumatic calculi which form after an injury to the spine with associated paralysis of the bladder or of the entire urinary tract. He pointed out that calculi are relatively uncommon after direct trauma to the kidney inasmuch as it is an exceedingly rare complication of the most common type of traumatic injury, i. e., operations on the kidney. He maintained that the blood clot which accompanies or follows an injury to the kidney does not alone suffice to explain the formation of calculi since the clot is often changed or even absorbed

while the stone forms, but that there must be, in addition, a disturbance of the colloid-crystalloid equilibrium of the urine with resultant precipitation of the urinary salts about a central nucleus or framework of red blood cells or fibrin in a blood clot. The calculi which develop after an acute trauma to the kidney are more loosely constructed than an ordinary laminated stone, and often a transverse section of a true traumatic calculus shows a small central cavity which is due to a resorption of the blood clot.

Oehlecker recently reported an interesting case of stone formation following a fracture of the third lumbar vertebra with avulsion of the transverse processes of this vertebra in addition to other severe bone fractures. Block reported a case of renal calculi developing in a man 33 years old after an injury to the cauda equina associated with paralysis of the bladder which followed a fall from a scaffolding for a distance of 23 meters. Simon reported an interesting case of a wounded aviator whose left kidney was shattered through a machine gun injury and who at the same time sustained a fracture of the first and second lumbar vertebrae. The left kidney was removed immediately. Subsequently calculus formed in the other kidney, and thirteen years later he succumbed to anuria.

Lesions of the kidney following spinal injuries are the result of paralysis of the bladder, ureter and renal pelvis. Holländer explained the bilateral formation of renal calculi following injuries of the cord on the basis of an interruption of the reflex arc concerned in the expression of urine from the renal papillae into the renal pelvis. He maintained that there is a loss of muscular activity in the renal pelvis and ureter, so that instead of the action as of an aspirator and pressure pump in the passage of urine from the renal papillae to the bladder, there is a slowing of the outflow of urine. This derangement of the nervous mechanism of the bladder, ureter and renal musculature favors urinary stagnation and infiltration with a resulting cystopyelitis or pyelonephritis. Secondary changes in the urine soon occur, i. e., decomposition and ammoniacal fermentation of urinary salts with ultimate formation of phosphatic calculi. Seefisch stressed the rôle of infection of the urinary passages in the formation of calculi following spinal injuries. The process involved in renal lithiasis following vertebral injuries has been considered by some workers to be similar to that in the formation of gallstones. Kocher believed that the increased elimination of calcium salts following spinal injuries is the cause of the formation of calculi. Haumann maintained that vasomotor paralysis is the chief factor in cases of calculi associated with transverse myelitis. The vasomotor paralysis causes hyperemia in the paralyzed parts and simultaneous anemia in the kidneys. Consequently, epithelial cells are shed by the

kidney forming a center for precipitation of calcium salts and especially phosphates.

Zondek stated that the stones seen after injuries of the spine are always particularly rough and irregular. He suggested that when such shadows are found in a roentgenogram of the kidneys the possibility of an antecedent spinal injury should be ruled out.

It is interesting to note that Rosenstein recently reported a case of bilateral renal lithiasis developing after a gunshot injury of the brain, which is apparently without an analogy in medical literature. In a case that we observed there was a history of fracture of the skull associated with a mangling injury to the right arm which was followed by the formation of calculi in the bladder and both kidneys. Thorn reported a case of recurrent calculus in a paraplegic patient.

The presence of calcium stones following injuries of the vertebrae and cord has been attributed to the absorption of calcium from the surfaces of the fractured vertebrae and from the long bones of the extremities, as manifested by the high degree of bone atrophy in these cases. The immobilization of the body following fractures of the spine favors such absorption, as emphasized by Lepoutre and Schwarz. Various authors have stressed the danger and influence of catheterization and cystostomy on the development of urinary infections and subsequent formation of stones in these cases.

The true significance of the tendency to deposition of calcium after vertebral fractures as a result of the disintegration of calcium salts remains as yet unexplained, as evidenced by the different conceptions of the authors cited. However, new information which may have a bearing on the question of the elimination of calcium through the kidney and its deposition in the renal pelvis or parenchyma has been contributed by Hess and his associates. They found that a marked rise and disturbance in the equilibrium of the calcium in the blood were brought about by section of the spinal cord in the upper dorsal segment. They also noted that the equilibrium of the calcium and the phosphorus in the blood serum was rendered less stable by division of the sympathetic or parasympathetic nerves.

Trosler recently submitted a clinical report of 19 cases of fracture of the transverse processes of the vertebrae producing symptoms simulating those referable to the kidneys. None of the patients showed evidence of renal calculi on roentgen examination.

#### FRACTURES AND TUMORS OF THE BONY PELVIS AND LONG BONES

The development of urinary calculi following fractures of the bony pelvis and of the long bones is perhaps a more common occurrence than a review of the literature would lead one to believe. A natural reluctance

on the part of urologists to report such isolated cases may account for the decided paucity of recorded observations.

Fractures of the bony pelvis are frequently accompanied by infection of the urinary tract. The infection may develop as a result of an associated injury of the bladder or urethra or as a result of the inactivity and lowered resistance accompanying the prolonged immobilization for the bone injury. The infection is usually present in the form of an ascending cystopyelitis. Noland and Conwell recently noted the apparent tendency toward infections of the urinary tract with formation of renal and vesical calculi during the convalescent period in several cases of severely fractured pelvis. Young and Waters, Cabot and Braasch and others have reported cases of urinary calculi following fractures of the pelvis.

The development of urinary calculi following fracture of a long bone, i. e., the femur, tibia, fibula, humerus, etc., is relatively infrequent. The exact etiologic relationship between the fracture and the urinary lithiasis is not definitely established. Bonneau and W. Weber reported cases of fracture of the long bones of the leg complicated by the formation of urinary calculi.

Wilson recently reported an interesting series of cases of renal colic and hematuria following recumbency for fracture of a femur. Of 150 patients treated by the Sinclair method, 23 (15 per cent) had renal colic. Most of the patients concerned were kept recumbent for a long time on account of severe wounds, prolonged sepsis and delayed union or nonunion. It was strikingly noticeable that in nearly all the cases renal colic and hematuria occurred suddenly on the first and second days after the patient got up and that the patient just as quickly got well again without fever, rigors or other trouble up to two and a half years afterward. In only 1 of the 23 cases was there evidence of calculus formation. The patient was a badly wounded man with an additional gunshot wound of the hip joint and was on his back for a long period with persisting local sepsis.

We have been unable to find in the literature any report of an association of urinary calculi with a tumor of the bony pelvis or a long bone with the exception of Jeck's case. He reported a case of multiple enchondromas involving the pelvic bones, femurs, tibia, fibula, radius and ulna of a male Negro 40 years old, which was complicated by calculi in the bladder.

Peterson reported some interesting observations on the calcium-phosphorus balance during the healing of fractures which may offer a solution to the problem. He noted a definite rise in the calcium-phosphorus product during the healing stage in the usual case of fracture. On the other hand, he found a reduction in this product in

those cases in which nonunion resulted, mechanical factors having been excluded. When the calcium-phosphorus product was below 30 the bones did not unite. When the product was between 30 and 35 there was little healing, but when it was between 35 and 40 the healing was very active. Thus one may infer that the metabolism of calcium and phosphorus is altered following a fracture of any long bone. Although Peterson's work appears to have been generally accepted, liberally quoted and literally interpreted, Speed failed to confirm these findings after studying several hundred observations on the blood serum calcium and phosphorus in a consecutive series of patients with fractures.

If these changes in the metabolism of calcium and phosphorus, however slight, are accompanied by faulty elimination through the kidney renal calculi may develop. The impaired renal function may be the result of a disease of the kidney antedating the fracture. A contributory factor may be the development of a renal infection during the period of immobilization for the fracture. Such an infection frequently occurs in elderly patients.

**CASE 7.**—R. S., a white woman 52 years old, married, a housewife, was admitted to Sinai Hospital on July 30, 1928, with a complaint of pain in the left side of the abdomen. She had always enjoyed good health until in December 1924, when she fell and sustained a fracture of the right femur. She began to have renal colic on the left side in March 1925 and again in May 1925. She was examined in August 1925, and a small calculus was found in the ureter. She thinks she passed this stone. Since December 1924 she has been using crutches to aid her in walking.

*Present Illness.*—About one week prior to examination she had a severe attack of renal colic on the left side, which lasted several hours and was relieved only after a hypodermic injection of morphine. The attack was accompanied by nausea, vomiting, chills and fever. There was diurnal and nocturnal frequency but no burning, dysuria, intermittency or hematuria.

*Physical Examination.*—A deformity was present in the right thigh due to an overriding of the fragments. There was definite tenderness in the left lumbar region and in the left upper quadrant of the abdomen.

*Laboratory Studies.*—A voided specimen of urine was negative for albumin and sugar but showed a few pus and red blood cells. The blood urea was 32.9 mg. per hundred cubic centimeters.

*Course.*—Cystoscopic and pyelographic studies revealed a small calculus the size of a pea at the junction of the middle and upper third of the left ureter. Several dilatations of the ureter were performed and the patient passed the calculus. She underwent an operation for realinement of the displaced ends of the right femur in the spring of 1929. There has been no further recurrence of the urinary symptoms.

*Diagnosis.*—The diagnosis was (1) left ureteral calculus and (2) fracture of right femur.

**CASE 8.**—C. R., a white man 50 years old, married, a machinist, was seen for the first time on Dec. 13, 1933, complaining of pain in the left lower quadrant of the abdomen. About ten weeks prior to this the patient sustained a compound

fracture of both bones of the left leg in an automobile accident. He was confined to bed for eight weeks and for three weeks had been walking with crutches.

*Present Illness.*—Four days before examination he had a sudden sharp pain in the left lower quadrant of the abdomen which radiated up to the left lumbar region and to the umbilicus. The pain lasted several hours, and morphine was required for relief. He had a similar attack on each of the following days. There were no urinary symptoms.

*Physical Examination.*—The positive findings were tenderness in the left lumbar region, the left upper quadrant of the abdomen and the suprapubic area.

*Laboratory Studies.*—A voided specimen of urine revealed only an occasional pus cell.

*Course.*—Cystoscopy and pyelography were performed on Dec. 31. Plain and stereoscopic roentgenograms with the catheter in the left ureter showed a small calculus in the lower third of the ureter. A left ureteropyelogram revealed a normal pelvis with a slight dilatation of the ureter above the stone. When the left ureteral catheter was withdrawn a small calculus, the size of the head of a match, was drawn into the bladder. This calculus was removed five days later. The patient has subsequently been free from symptoms.

*Diagnosis.*—The diagnosis (1) was left ureteral calculus and (2) compound fracture of the left leg.

CASE 9.—F. H. K., a white man 45 years old, married, was first seen on Aug. 8, 1933, complaining of pain in the left side of his back. In 1896 he sustained a fracture of both bones of the left leg as a result of a horse stepping on his leg, and in 1908 he incurred a similar fracture in an automobile accident. Following the latter injury he walked with a decided limp.

*Present Illness.*—One year prior to examination he began to have renal colic on the left side, which was followed by expulsion of a small stone. He had recurrent attacks of sharp pain in the left lumbar region which occasionally radiated to the left groin. He also complained of burning, urgency, frequency, etc.

*Physical Examination.*—The results were negative except for slight tenderness in the left lumbar region and a first degree enlargement of the prostate. A voided specimen of urine showed only a few pus and red blood cells.

*Course.*—Cystoscopy was attempted on Aug. 8, 1933, but was impossible owing to an obstruction at the vesical orifice. Intravenous urography revealed a normal renal pelvis on the right and mild hydronephrosis and hydro-ureter on the left. No stones were visible in the kidneys or ureteral regions. After several dilatations of the vesical orifice, cystoscopy and pyelography performed on December 20 revealed marked stenosis of the vesical orifice, two vesical diverticula and hydronephrosis on the left. The patient was admitted to the hospital, and the vesical diverticula and the prostate were removed in a two stage suprapubic operation. The convalescence was uneventful. However, the pain in the left lumbar region persisted. On June 16, 1934, a plain roentgenogram revealed a small shadow on the left side opposite the transverse process of the second lumbar vertebra. Several days later the patient passed a small stone.

*Diagnosis.*—The diagnosis was (1) left ureteral calculus (passed), (2) old fracture of the left tibia and fibula, (3) benign hypertrophy of the prostate and (4) left hydronephrosis.

CASE 10.—This case is reported through the courtesy of Dr. John Hogan. H. T., a white girl aged 9 years, sustained a fractured pelvis in June 1932. In



July 1934 she was admitted to the hospital, complaining of pain of four months' duration in the left side of the abdomen. An appendectomy was performed. Following the operation the pain persisted, and the patient was readmitted to the hospital on September 24. There were no urinary symptoms.

*Physical Examination.*—The positive findings were tenderness in the left lower quadrant of the abdomen and the left lumbar region. The urine showed a slight trace of albumin and an occasional red blood cell.

*Course.*—A plain roentgenogram of the genito-urinary tract showed a small irregular shadow opposite the ischial spine on the left side. The presence of a stone in the left ureter was confirmed by cystoscopy (fig. 5). Intravenous urography showed normal kidneys and pelves. On the third day following cystoscopy, she passed a calculus.

*Diagnosis.*—The diagnosis was (1) left ureteral calculus and (2) fractured pelvis.

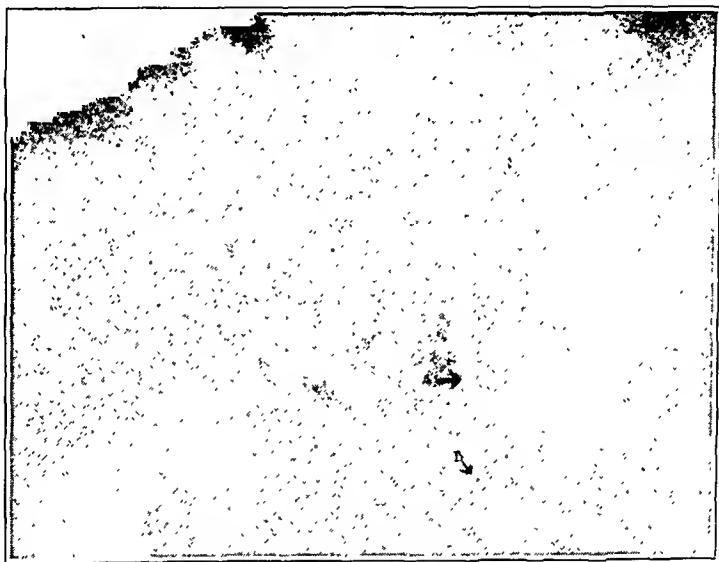


Fig. 5 (case 10).—Roentgenogram showing a calculus in the left ureter, indicated by A, and the site of an old fracture in the ischium, indicated by B.

#### OSTEITIS FIBROSA CYSTICA

Osteitis fibrosa cystica, often spoken of as osteitis fibrosa, is also more common than is generally supposed. The essential features were first described by von Recklinghausen in 1891; hence the disease frequently bears his name.

The disease is more frequent in females and is encountered in childhood and adolescence. Although the majority of the cases occur in patients under 20, cases have been reported which occurred in adults and elderly people. The onset is insidious, usually painless, the disease producing few early symptoms. Attention is first called to the disease by the occurrence of a spontaneous fracture or fracture following an unusually slight injury. The long bones are the most common site of

the lesion, and in the order of frequency of involvement one notes the humerus, femur and tibia. The jaw, skull and pelvis may also be involved.

Two types of the disease are recognized, i.e., a localized and a generalized type. The localized form may be accompanied by a benign bone cyst and is dependent on trauma in the majority of instances. The generalized form is dependent on grave nutritional or metabolic disturbances. Dysfunction of endocrine glands, faulty calcium metabolism and chronic infection of a low grade appear to have some etiologic significance. A striking relationship exists between osteitis fibrosa cystica and tumors of the parathyroids.

The disturbed calcium metabolism in this disease was first described by Jacoby and Schroth and was later observed by Dawson and Struthers, Huepner, and Hubbard and Wentworth. Jacoby and Schroth found an abnormally high excretion of calcium, which they thought could be remedied by administration of calcium lactate. Mandl, Gold, Wilder, Boyd and others have also noted the increased excretion of calcium in the urine which is reduced after operative removal of an associated parathyroid tumor. Studies of the calcium in these patients usually revealed hypercalcemia. The calcium content of the serum ranged from 12.8 mg. per hundred cubic centimeters in Snapper's case. A co-existing hypophosphatemia has also been observed in several cases.

Calcium stones in the upper urinary tract have been reported in several cases of osteitis fibrosa cystica. Gaugele's patient, a woman aged 37, died of uremia, and at autopsy the kidneys were found to contain sand and stone which had caused hydronephrosis and pyelonephritis. Stones were also present in the ureter. In the case presented by Hoffheinz, calcium infarcts as well as a large coral stone in the upper calyx of the right kidney were found.

#### OSTEOMALACIA

Osteomalacia is a chronic disease of the bones and is frequently known and described as fragilitas ossium and as osteoporosis. The disease is most frequently seen in pregnant women, especially at the puerperium or at the height of reproductive activity in the third decade.

The bones are soft, the consistency varying from that of wax to that of wet paper, according to the loss of mineral constituents. The bones show many deformities and often present old or new fractures. On section, a reduction of the compact and cancellous tissue with cavity formation is noted in addition to changes in the marrow of a hemorrhagic or lymphoid nature.

In the cases reported there was an obvious lack of mineral elements in the food due to the absence of vegetables, cheese, fish, butter, eggs, rice and meat, all of which are normal sources of calcium and phosphorus. With such dietary deficiencies the vitamins are necessarily reduced. Softening of bones has long been known to occur experimentally in animals with defective nourishment. Van Saceghem also noted its occurrence in various animals in the Belgian Congo where the water is lacking in calcium and phosphorus.

Miles and Feng studied osteomalacia in females in China whose diets were deficient in fat-soluble vitamins and described deformities similar to those of rickets. They found that the calcium of the blood serum was greatly reduced, varying between 5.8 and 7.5 mg. per hundred cubic centimeters, the normal value being from 10 to 11 mg.

In the literature there are very few references to the occurrence of renal calculi in cases of osteomalacia. The development of urinary calculi in association with osteomalacia was pointed out by Steibel and Senator. They believed that in this disease the inorganic salts of the bone are removed and eliminated in especially large quantities in the urine. The earliest report was that by Solly in 1844. He found a large calculus of calcium phosphate in the kidney of a woman 39 years old who had died of generalized osteomalacia. He explained the formation of calculi on the basis of the absorption of the earthy matter of the bones and its excretion through the kidney in such abundance that it clogged the pelvis and calices. In 1864, Durham reported a case of *mollities ossium* (osteomalacia) in a woman, aged 49, whose kidneys were found at autopsy to be apparently normal except that one contained a small calculus in a pouch connected with its pelvis.

Dereux cited the case of a young woman, aged 17, who had suffered from infantile osteomalacia and in whom calculi were discovered in the bladder and kidneys on roentgen examination. Bouley is quoted by Dereux as having seen cases of renal calculi associated with osteomalacia.

#### OSTEOGENESIS IMPERFECTA AND OSTEOPSATHYROSIS

Osteogenesis imperfecta is a rare systemic disease of the bones. The disease is characterized by an imperfect development of the osseous systems as evidenced by stunted growth, a deformed skull and frequent fractures with excessive callus formation. There is a marked loss of calcium and phosphorus from the bones. Some attribute this derangement of calcium metabolism to a dysfunction of the endocrine glands, especially of the thymus and parathyroids. "Osteopsathyrosis" is the name applied by Lobstein (1883) to various types of bone fragility some of which are identical with osteogenesis imperfecta and others of which for a long time were incorrectly considered as osteomalacia or rickets.

In a careful perusal of the literature we could not find any record of the occurrence of renal calculi in association with osteogenesis imperfecta and only an occasional report or reference to their occurrence with osteopsathyrosis. The disturbances in calcium and phosphorus metabolism occurring as a result of the bone lesions in these diseases would favor the formation of renal calculi.

Taterka and Dinkin recently reported a case of nephrolithiasis associated with osteopsathyrosis in a man 41 years old. In a later discussion of this case Dinkin stated that there was a disturbance of hormonal equilibrium with a resultant disturbance of mineral metabolism which was favorable to stone formation.

#### RICKETS

In the past ten years remarkable progress has been made in the diagnosis and treatment of pathologic conditions of the urinary tract in children. With the increasing attention of physicians and surgeons to these conditions and the perfection of urologic technic, i. e., roentgenography, cystoscopy, retrograde and intravenous pyelography, etc., many of the hitherto baffling urologic conditions in children are now correctly diagnosed and properly treated.

The association of various infectious diseases with urinary calculi in children was definitely established by H. Joseph. He also reported 6 cases of rickets in which urinary calculi were observed. In these 6 cases, 4 were bilateral and 2 unilateral (both in the right kidney). W. Weber, Brown, Taterka and Dinkin each reported a case of urinary calculus associated with rickets.

In the literature one finds an occasional reference to the etiologic relationship between rickets and urinary calculi. Federoff and Rubritius attributed the formation of calculi in cases of rickets to the occasional increase of mineral salts in the urine.

A rather ingenious but plausible explanation for the development of renal calculi in rickets is offered in an editorial in the *Southern Medical Journal* (21: 162 [Feb.] 1920): The relation of the acid-base balance of the intestinal tract to the deficient assimilation of calcium and phosphorus in rickets is particularly stressed. It is pointed out that an alteration in the acid-base balance of the intestinal tract in rickets may be accompanied by a comparable acid-base disturbance in other tissues of the body, especially in the bladder and kidney, which may interfere with the normal excretion of phosphorus and calcium and favor stone formation.

Undoubtedly, many of the cases of renal lithiasis in children and young adults will reveal antecedent rickets if care is exercised in obtaining an accurate history. This interrelationship has not been emphasized

strongly enough. In the treatment of these conditions careful attention should be paid to the diet. The diet should contain adequate amounts of milk, cream, butter, fresh fruits and vegetables, as not infrequently the diet of children is a mildly rachitic one. The importance of a sufficient amount of vitamins A and D in the diet in the prevention of renal calculi and urinary infections is borne out by the work of Fujimaki, McCarrison and van Leersum.

#### TUBERCULOSIS OF THE BONES AND JOINTS

The presence of renal calculi following or during a suppurative tuberculous lesion of the bone may be dependent on the development of a tuberculous renal lesion. This may be a nephrosis accompanied by faulty elimination of inorganic salts or a tuberculous nephritis which may subsequently undergo caseation and abscess formation with frequent bacilluria. The renal calculi may develop as a result of stasis and infection of the urine secondary to the immobilization and infectious process which accompany the bone lesion. A contributing factor may be a faulty elimination of the mineral salts which are altered by the bone lesion. However, there are frequent references in the literature to renal calculi occurring in tuberculous kidneys. Liebermeister found tubercle bacilli in renal calculi and stated that the coincidental occurrence of a tuberculous lesion of the kidney and renal calculi is more frequent than is generally believed.

Mayet reported a case of bilateral renal lithiasis in a 7 year old boy who had suffered with Pott's disease of the spine. He also reported a second case occurring in a girl, aged 14 years, who had a tuberculous hip with an abscess which was aspirated. She had been treated by immobilization for two and one-half years when she was seized with an attack of renal colic and passed a small calculus. Iselin reported the case of a patient, aged 30 years, from whom, following twenty-two months of immobilization for a tuberculous knee, a uric acid calculus in the right kidney was removed by pyelotomy. Mayet believed that the formation of such calculi in cases of tuberculosis of bones or joints is secondary to renal tuberculosis and considered the immobilization for the spinal disease and the ingestion of excess phosphates as contributory factors.

W. Weber observed the formation of a calculus in a patient 19 years old who had been treated for left tuberculous coxitis. In the discussion of Weber's paper, Grossman reported the occurrence of urinary calculi in 6 cases of tuberculosis of the hip and in 3 cases of Pott's disease of the spine. Lepoutre reported a case of bilateral nephrolithiasis developing in a man 25 years old who had been under treatment for twenty-one months for Pott's disease of the spine and arthritis of the

left knee and toes which required long immobilization. He also observed another case of bilateral nephrolithiasis in the course of a tuberculous lesion of the spine.

Grunert and Berger recently observed the formation of renal calculi in 12 of 250 patients with chronic inflammatory osseous lesions, 10 of whom were tuberculous. Young reported a case of long-standing complete destruction of a kidney due to calculi in a young man complaining of a sinus in his left lumbar region. Unfortunately, the patient had undergone a previous operation for supposed tuberculous disease of the spine, and the sinus discharged a seropurulent material.

**CASE 11.**—M. V., a woman aged 41, single, was first seen in the outpatient clinic of Sinai Hospital on May 22, 1928, with a complaint of pain in the right upper quadrant of the abdomen and indigestion. The family history was negative except that there was a definite history of tuberculosis in her paternal relatives. One cousin and a paternal aunt with whom the patient had some contact had pulmonary tuberculosis. At the age of 18 months the patient fell and injured her right hip. At the age of 8 years she was admitted to Johns Hopkins Hospital and an operation was performed on her right hip for a tuberculous infection of the joint. Between 1920 and 1929 she had several operations for tuberculous osseous lesions. In 1925 she had thirteen cystoscopic treatments. During this time several calculi were passed. She had been using crutches for the past fifteen years.

*Present Illness.*—The patient was referred to our clinic for cystoscopic treatments. She was suffering from diurnal frequency and nocturia. There was no definite history of renal colic or hematuria. She also complained of sharp pain in the right upper quadrant of the abdomen radiating upward to the right shoulder and occasionally toward the right shoulder blade. Her appetite was poor, and at times there were nausea, vomiting, belching and constipation. There were no clay-colored or tarry stools at any time. Her menstrual periods were always normal in regard to periodicity, flow and pain.

*Physical Examination.*—At the time of her admission to our clinic in May 1928 examination disclosed the following positive findings: She was of short stature, fairly well nourished and obviously deformed. She had marked scoliosis of the lumbar spine to the left with a tilting of the pelvis to the right. There was complete ankylosis of the right hip with only partial motion in the left hip (fig. 6A). The abdomen was full and round with tenderness in the right upper quadrant on deep palpation.

*Course.*—Cystoscopic studies revealed bilateral ureteral strictures with an accompanying moderate hydronephrosis on each side. There was no evidence of renal or ureteral calculi. There were no signs of tuberculosis on cystoscopic and pyelographic studies. Examinations of the urine, cultures and guinea-pig inoculations gave no evidence of the presence of tubercle bacilli.

She was then lost sight of and we next learned that she had a cholecystectomy performed in the latter part of 1929 at another hospital. She also had an exacerbation of the trouble in her right hip in the fall of 1930 which required incision and drainage, and she was confined to bed for one month. Two months later she began to complain of sharp colicky pain in the right lumbar region radiating to the groin and accompanied by frequency, urgency, dysuria and a burning sensation

on urination. Cystoscopic and roentgenographic examination revealed a stone in the lower third of the ureter which produced a scratch on a wax-tipped catheter (fig. 6*B*). After one dilatation of the right ureter (no. 10 French) the stone was passed. A roentgenogram taken in August 1932 revealed a small stone in the right kidney. At present the patient is confined to a sanatorium because of active pulmonary tuberculosis.

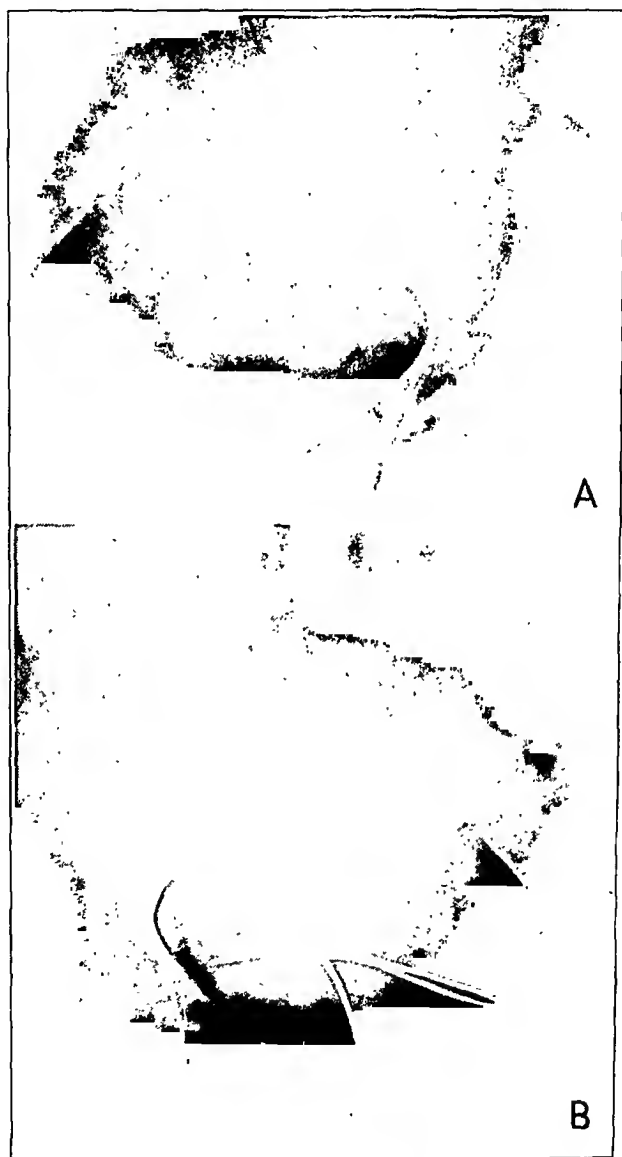


Fig. 6 (case 11).—*A*, marked deformity of the pelvis with rotation of the lumbar portion of the spine due to an old tuberculous process in both hip joints. Rarefaction of both ilia may be seen. There is absence of the head of the right femur with fixation of the upper end of the femur above the acetabulum. *B*, essentially the same bony changes as in *A*. The shadow seen above the tip of the catheter is a calculus in the lower third of the right ureter.

*Diagnosis.*—The diagnosis was (1) right renal calculus, (2) pulmonary tuberculosis and (3) tuberculosis of both hip joints.

## ARTHRITIS

There have been many descriptions of varieties and phases of arthritis and also many classifications of the types of arthritis based on clinical, etiologic or other factors. However, the recent classification of arthritis based on pathologic changes as advocated by the English investigators appears to be most practical. Arthritis has been conveniently classified by Jones into the following subgroups: rheumatoid arthritis and osteo-arthritis.

There are few reports in the literature concerning the occurrence of urinary lithiasis in arthritic patients. We have so frequently detected evidences of an infectious arthritis of the spine or hip joints during the course of roentgenographic studies of urolithiasis that we believe that they have a greater significance than that of mere coincidence.

One cannot fail to recognize the fact that a close relationship may exist between the two conditions as in some instances the same etiologic factor is involved in the production of both conditions. Urinary calculi developing in patients whose arthritis is the result of a genito-urinary lesion may be a coincidental finding with no direct relation to the arthritis. In such cases, the stone formation is or may be purely dependent on a lesion of the urinary tract. However, when arthritis results from a focus of infection in any part of the body other than the genito-urinary tract the organism producing the arthritis may also set up a urinary infection with subsequent formation of stone.

W. Weber and Payr are of the opinion that chronic infectious arthritis of the spine and that of the hips are diseases of the osseous system which show a particular tendency to lithiasis. Weber reported a case of nephrolithiasis occurring in a patient suffering from infectious arthritis of the hips. Roentgen examination disclosed the shadows of several calculi in the left kidney. Barr and Charles stated that they had observed renal calculi in 10 cases of osteo-arthritis of the spine. They also reported renal calculi in a 17 year old boy with proliferative arthritis of the joints of the hand, wrist, elbows and knees and in a 32 year old Negro with extensive destruction of the hip joint (Charcot's joint) and osteo-arthritis of the spine. A case report of ours is as follows:

CASE 12.—This patient was referred by Dr. M. B. Levin. H. B., a man 72 years old, married, a retired merchant, was seen for the first time at home on Oct. 3, 1932, complaining of frequency of urination. The family history was essentially negative except that his mother had died of intestinal carcinoma. He had pneumonia as a child and malaria at the age of 16 years. He had been treated for "rheumatism" and arthritis for the past twenty years. For the past few years he had received treatment for various foci of infection, which included diathermic treatment of the tonsils, removal of infected teeth, a nasal and a sinus operation. He stated that fifteen years ago he had renal colic but did not recall on which side the pain occurred. He passed a stone from his bladder thirty years ago.



*Present Illness.*—The onset of the present trouble dated back several months. He began to complain of frequency, urination occurring every hour during the day and three or four times at night, difficulty in starting his stream, straining, urgency, burning and intermittency. On two occasions in the past three months, acute retention of the urine developed and he had to be relieved by catheterization. He had chills and fever at irregular intervals in the past few weeks. He also complained of pain in both lumbar regions, more marked on the right than on the left side. The pain at times had been sharp, but for the past week had been dull and persistent. He occasionally had a dull pain in the suprapubic region.

The patient had been confined to bed for the past five years because of inability to move his lower extremities. He complained of pain in practically every joint in his body. His ankles, knees, elbows and wrists were markedly enlarged, swollen and tender. He stated that his arthritis was becoming progressively worse.

*Physical Examination.*—The patient was a very stout, obese male. He was unable to stand because of the pain from pressure attending movements of his joints. His head was markedly enlarged. There was a deformity of the elbows, wrists and joints of the fingers. The abdomen was very obese. Neither kidney was palpable. There was slight tenderness in the right lumbar region but no tenderness over either kidney or ureter anteriorly. Rectal examination disclosed benign hypertrophy of the prostate, of the first degree.

*Laboratory Studies.*—A voided specimen of urine was acid in reaction and had a specific gravity of 1.020. Tests for albumin and sugar were negative. Microscopic examination revealed many pus cells and red blood cells.

*Course.*—A plain roentgenogram of the genito-urinary tract revealed a shadow the size of a walnut in the region of the bladder. Under caudal anesthesia, the vesical calculus was crushed and removed. Two weeks later the patient returned, complaining of pain in the region of his right kidney following an automobile ride. A roentgenogram of the genito-urinary tract revealed a shadow the size of a lima bean in the region of the lower part of the right ureter (fig. 7A).

Roentgen studies of the skull, pelvis and spine were made and showed the typical osseous changes of Paget's disease (fig. 7B).

*Diagnosis.*—The diagnosis was (1) vesical calculus, (2) right ureteral calculus, (3) arthritis deformans and (4) Paget's disease.

The evidence concerning the occurrence of a disturbance in the calcium metabolism is conflicting. In 1894 von Noorden and Belgardt and in 1910 Hofmeister found some evidence of a negative calcium balance in a small number of cases of osteo-arthritis. In 1904 McCrudden found a marked negative calcium balance in cases of atrophic arthritis, and a positive balance in cases of hypertrophic arthritis. However, a number of investigators using the newer and improved quantitative methods for the determination of calcium in small amounts of blood are still at variance in regard to the presence or absence of hypercalcemia.

Reports of hypercalcemia in arthritis have been contributed by several investigators. Weill and Guillaumin, in their study of a series of 11 cases of chronic arthritis, reported serum calcium values ranging from 11 to 17.8 mg. per hundred cubic centimeters as compared with the

normal values of from 9 to 11 mg. Watchorn likewise found the serum calcium slightly elevated in chronic arthritis. Horowitz found values as high as 16.2 mg. in 5 of 14 cases of arthritis with severe deformities. Mark reported 4 cases in which the calcium values for the whole blood ranged from 13.3 to 20.3 mg.

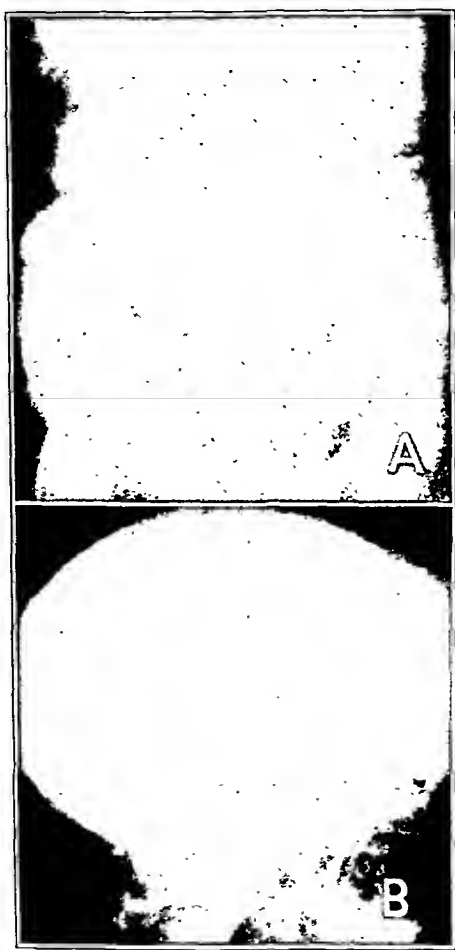


Fig. 7 (case 12).—*A*, roentgenogram showing the large calculus in the bladder. The pelvic bones and vertebrae show changes due to osteitis deformans. *B*, roentgenogram showing typical changes of osteitis deformans in the skull.

Nachlas, however, was unable to find hypercalcemia in 19 cases of osteo-arthritis or in 18 cases of rheumatoid arthritis. Hench and Rentschler failed to find hypercalcemia in 25 cases of infectious arthritis at the Mayo clinic. Koenig and Bulger likewise were unable to demonstrate hypercalcemia in 30 arthritic patients. Pemberton and his

associates studied the calcium metabolism in arthritic conditions of long duration with limitation of motion and with ankylosis, the type of case in which Mark and also Weill and Guillaumin found high serum values. Their studies gave figures for serum and plasma calcium within the limits usually ascribed to normal blood.

#### SPONDYLITIS DEFORMANS

This disease is a form of arthritis deformans occurring more often in males than in females. The spinal involvement may be present alone or associated with involvement of peripheral joints. Spondylitis deformans may be the result of repeated acute attacks or of a chronically progressive process and is characterized by bony proliferation causing rigidity of the spinal column.

Grossman stated that among the last 1,000 cases of lithiasis observed in the urologic section of the Hedwig Hospital in the past fifteen years there were 14 cases in which lithiasis was concurrent with diseases of the bone. Among these 14 cases were 6 of arthritis deformans of the spinal column and 2 of spondylitis deformans of the Bechterew type. Eisenstaedt reported that the largest stone he has removed from the bladder was in a patient suffering with severe spondylitis deformans. Schwarz stated that he recently observed a case of traumatic spondylitis deformans (Bechterew's disease) with bilateral nephrolithiasis. Barr and Charles reported the development of multiple calculi in a man 71 years old who had a deformity of the spine resulting from an old destructive lesion of the fourth lumbar intervertebral disk and hypertrophic osteo-arthritis.

Israël recently reported a case of bilateral renal lithiasis in a man 38 years old who suffered with ankylosing spondylarthritis of the Strümpell-Marie type. Roentgen studies showed extensive formation of calculi in both kidneys. Israël discussed the possible factors responsible for the simultaneous occurrence of the two disease processes—the ankylosing spondylarthritis and the bilateral nephrolithiasis—and maintained that the stone formation was dependent on the disease of the spinal column; i. e., he did not believe that both diseases could be attributed to common causes or conditions. In his opinion the factor that influenced the production of renal calculi in the disease of the spine was a disturbance of calcium metabolism as manifested by the increased calcium content of the blood and the increased amount of calcium in the urine. Although such a disorder of metabolism is more common in bone destruction, it may occur in any process of pathologic bone formation, in which category this disease belongs.

## NEPHROGENOUS SCOLIOSIS

In 1926 Carty emphasized the diagnostic significance of lateral curvature of the spine caused by muscular spasm. He pointed out that a lumbar scoliosis should direct attention to a renal stone, hydronephrosis or perinephritic abscess, possibly not suspected. He found this deformity in 60 per cent of 100 patients with large renal calculi and stressed the fact that the presence of a lateral deformity may be of considerable importance since this type of calculus may give rise to little or no pain or other symptoms.

In a recent article Blumensaat and Nestman also called attention to the fact that in most cases of renal disease there is an accompanying scoliosis of the lumbar segment of the spinal column. They suggested the use of the term "nephrogenous scoliosis" in preference to the older term "nephritic scoliosis." They found that in cases of renal calculus the curve is convex to the stone; in hydronephrosis, pyonephrosis, pyelitis, tuberculosis, paranephritis and mobile kidney it is concave to the lesion; in cases of tumor the direction of the scoliosis is variable. They maintained that in cases of stone the scoliosis is the result of a protective action whereas in cases of hydronephrosis it is a mechanical response, and in the remaining cases it is caused by the contraction of the muscles on the diseased side.

In 1931 Nuvoli and Impiombato reported 150 cases of malformation of the spine accompanied by the syndrome of urinary calculosis. They examined 150 cases with this syndrome and found calculi in only 26 cases. In all except 16 of the 150 cases there was some malformation of the spine, i. e., lumbarization of the twelfth dorsal vertebra, dorsalization of the first lumbar vertebra, sacralization of the fifth lumbar vertebra, lumbarization of the first sacral vertebra and spina bifida. Milliken reported a case of nephrolithiasis associated with marked scoliosis in a man 25 years old.

CASE 13.—S. W., a white man 34 years old, a salesman, was admitted to Sinai Hospital on July 26, 1924 with the complaint of pain in the right lower quadrant of the abdomen and right side of the back. The family history was unimportant. The patient had a gonorrheal infection at the age of 20 and subsequently an infection in his prostate for which he was treated. The patient stated that in 1919 he had severe colicky pain in his right side, and that an appendectomy was performed but that a normal appendix was found. Five days after the operation he had a similar attack of pain.

*Present Illness.*—A sudden sharp pain developed in the lower right quadrant of the abdomen radiating to the right testicle two weeks prior to examination. The pain lasted several hours but was not accompanied by nausea, vomiting, chills or fever, nor did it require morphine for relief. There were no symptoms of frequency, urgency, tenesmus, hematuria, etc.

*Physical Examination.*—The results were essentially negative except for tenderness in the right lower quadrant over the course of the right ureter. There

was marked scoliosis of the dorsal spine with elevation of the right shoulder and general spasticity of all the spinal muscles.

*Laboratory Studies.*—A voided specimen of urine was negative for albumin and sugar, but on microscopic examination showed a few pus and red blood cells.

*Course.*—On July 26 cystoscopic and pyelographic study revealed a small calculus in the upper third of the right ureter. Five days later the patient passed a small stone.

The patient failed to return for observation and treatment until July 9, 1928, when he presented himself complaining of pain in the right renal region. Eight weeks previously he had an attack of right renal colic accompanied and followed by diurnal frequency and nocturia but not by hematuria, dysuria or burning. A roentgenogram of the genito-urinary tract taken at this time showed a shadow in the region of the right kidney. The patient was not seen again until Oct. 9,



Fig. 8 (case 13).—Plain roentgenogram showing marked scoliosis with deviation away from the affected side. The shadow seen above the catheter in the eleventh right intercostal space is a calculus in the right kidney.

1929, when he was admitted to the hospital for further study. Cystoscopic and pyelographic studies revealed a calculus in the right renal pelvis (fig. 8). On October 18 a right pyelolithotomy was performed under gas anesthesia, and the calculus was removed. The calculus measured approximately 1.5 by 1 by 0.5 cm. and was reddish yellow and firm with an irregular, warty surface. He made an uneventful recovery. When last seen on July 9, 1931 he was in excellent health.

*Diagnosis.*—The diagnosis was (1) calculus in the right kidney and (2) scoliosis.

**CASE 14.**—L. L., a white woman 66 years old, Jewish, a widow and housewife, was referred by, and her case reported through, the courtesy of Dr. S. Lubash of New York. On May 6, 1934, while in New York, the patient was seized with sharp pain in the left upper quadrant of the abdomen. Dr. Lubash performed a cystoscopic and pyelographic study and found a large nonfunctioning calculous pyonephrotic kidney on the left side. The condition of the patient was poor and

an emergency nephrostomy was performed, at which time a large calculus and about a pint (about 473 cc.) of thick pus were removed. The patient made an excellent recovery, and at the time of discharge from the hospital roentgen studies revealed no evidence of urinary calculi. She returned to her home in Baltimore with the wound well healed and a properly functioning nephrostomy tube in place. Further cystoscopic studies revealed a marked restoration of function in the left kidney with a decided reduction in the size of its pelvis. The nephrostomy tube was removed on Sept. 27, 1934, and the wound closed promptly. A secondary nephrectomy does not appear to be necessary at this time.

The patient stated that she had had dull pains in the lumbar portion of the spine for ten years and had received treatment for hypertrophic arthritis and



Fig. 9 (case 14).—Roentgenograms showing marked scoliosis of the lumbar portion of the spine with deviation of the spine toward the left side. The left ureter is filled with dye up to the tip of the catheter, at which point a large calculus can be seen.

scoliosis of the lumbar part of the spine. A roentgenogram revealed marked scoliosis of the lumbar part of the spine with deviation to the left (fig. 9).

*Diagnosis.*—The diagnosis was (1) left calculous pyonephrosis and (2) scoliosis.

#### HYPERPARATHYROIDISM

Barr, Bulger and Dixon emphasized the relationship of parathyroid hyperplasia (adenoma) to the bone changes in osteitis fibrosa and called the clinical syndrome "hyperparathyroidism." They pointed out that

the symptoms of clinical hyperparathyroidism are similar to those produced by experimental injection of excessive amounts of parathyroid extract. They also stressed the following important clinical features: (1) hypercalcemia, (2) abnormal excretion of calcium in the urine, (3) hypertonia and muscular weakness, (4) decalcification and rarefaction of bones and (5) multiple cysts or tumors of the bones. The following features may also occur: hypophosphatemia, a negative calcium balance and nephrolithiasis.

In 1931 Hunter collected 32 cases of hyperparathyroidism and found renal calculi in 10 cases. In 1934 Barney and Mintz reviewed the literature and brought the total to 65 cases reported by 36 different authors. They found renal calculi in 15 cases (23.07 per cent); in 10 cases the calculi were bilateral. In addition, they reported the presence of renal calculi in 11 of 18 cases of hyperparathyroidism observed in a series at the Massachusetts General Hospital in which the diagnoses were confirmed by operation, as indicated in the report of Churchill and Cope. These 11 cases are included in a series of 104 cases of urinary calculi which Barney and Mintz have encountered since 1933 and studied particularly from the standpoint of changes in the blood calcium and phosphorus. They stated that parathyroid disease is the apparent etiologic factor in 10 per cent of the cases of urinary lithiasis.

#### RENAL RICKETS AND CHRONIC INTERSTITIAL NEPHRITIS IN CHILDHOOD

Chronic renal disease in infancy and childhood and the closely allied disease renal rickets have received considerable attention in British medical literature; only recently have they been discussed in French, German, Italian and American literature. The first to note the association of chronic renal disease with changes in the bones was Lucas, who in 1883 described late rickets and albuminuria in 5 patients.

The term "renal dwarfism" or "renal nanism" is employed to denote the small stature and stunted growth that may accompany chronic interstitial nephritis in early life. The term "renal infantilism" is applied to a chronic kidney disease in which faulty or complete lack of primary and secondary sexual development is a special feature. Mitchell in 1930 presented an excellent review of chronic interstitial nephritis in childhood and renal rickets, and we have drawn much of our information from his work on this subject. He was able to collect about 200 authentic cases of chronic interstitial nephritis in persons under 20 years of age. In 78 of these cases there were clinical or roentgenologic evidences of abnormal changes in the bones, to which he added 2 cases of his own, making a total of 80 cases of renal rickets. It is the latter group which particularly commands our attention in this paper.

The term "renal rickets" or "renal pseudo-rickets" is employed to designate the chronic interstitial nephritis in infancy and childhood which is accompanied by marked alteration in the growth of the bones and by various types of bony deformities. The amount of bone change and deformity is closely associated with the time of onset, duration and severity of the chronic disease of the kidney.

In renal rickets there is a disturbed relation between the calcium and the phosphorus of the blood. In the stage of active symptoms the calcium content of the blood is frequently below the normal level of from 10 to 12 mg. per hundred cubic centimeters and the inorganic phosphorus above the normal level of from 4.5 to 5.5 mg. The lowered blood calcium and the increased blood phosphorus serve to distinguish renal rickets from hyperparathyroidism, in which the reverse is true.

While the usual pathologic process in the kidneys in renal rickets is a chronic interstitial nephritis there are many cases in which the renal insufficiency is due to some other pathologic condition in the urinary tract. Mitchell stressed the fact that a functional insufficiency and symptoms similar to those produced by chronic interstitial nephritis may be caused by such lesions as congenital or acquired obstruction of the urinary tract, chronic infections, renal calculi and congenital renal anomalies.

Several authors (Goodhart, Barber and Parsons) have commented on the occurrence of renal calculi in renal rickets but have not given detailed reports of any cases seen by them. Davies-Colley reported a case of renal rickets in a 13 year old girl who had four impacted stones in the right ureter and a number of angular stones in the right kidney, which was the seat of multiple suppurative lesions. Zanolli reported a case in which a calculus in the bladder was demonstrated by roentgenogram. Mitchell stated that in a case which he observed there was a heavy amorphous deposit of salts in the tubules and pelvis of each kidney. Tuechter reported a case of renal calculus in a youth of 18 years, diagnosed as renal infantilism associated with hypothyroidism.

#### CONCLUSIONS

A review of the literature and a study of 14 personal cases of urinary calculi in association with various bone diseases warrant the following conclusions:

1. There appears to be a definite etiologic relationship between urinary lithiasis and various chronic bone diseases; consequently, in all cases of urinary calculi information concerning a previous bone injury or disease should be sought and carefully considered from an etiologic standpoint.



2. The development of urinary calculi during the course of chronic bone disease is uncommon though not infrequent.

3. Infection of the urinary tract secondary to acute or chronic infection of the bones or joints, i. e., arthritis or osteomyelitis, may be a predisposing factor in the formation of urinary calculi.

4. Urinary calculi may develop following injuries of the vertebrae and cord.

5. The formation of urinary calculi in the presence of rickets, osteitis deformans, osteomalacia, osteitis fibrosa of von Recklinghausen, osteitis fibrosa cystica associated with hyperparathyroidism and other diseases of bone appears to be dependent on a disturbance of the calcium-phosphorus metabolism which upsets the colloid-crystalloid equilibrium of the urine with subsequent precipitation and coalescence of the urinary constituents.

6. Careful attention should be paid to providing an adequate diet in the treatment and prevention of urinary calculi in all persons, especially those afflicted with chronic bone diseases, since a diet deficient in vitamin A and inorganic calcium and phosphorus is an etiologic factor in the formation of urinary calculi in the experimental animal and is reputed to be an etiologic factor in the clinical and experimental production of several types of chronic bone diseases, i. e., rickets, osteitis deformans and osteomalacia.

7. We report 14 cases of urinary calculi in association with bone diseases, viz.: 4 cases following amputation of the extremities; 2 following osteomyelitis; 3 following fracture of long bones; 1 following fracture of the pelvis; 1 following tuberculosis of the hip joints; 1 following arthritis deformans with associated osteitis deformans, and 2 associated with scoliosis.

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# CHRONIC NONSPECIFIC THYROIDITIS

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## INTRODUCTION

Chronic nonspecific thyroiditis is a nonsuppurative disease of unknown etiology, affecting the thyroid gland of men and women, both young and old. It is characterized by the rapid development of an extremely hard, frequently fixed tumor, without previous or present signs of hypothyroidism or hyperthyroidism, although a goiter may have been present for some time. There is little, if any, associated fever or leukocytosis. Pain is very infrequent, dyspnea, dysphagia and aphonia being the most common symptoms. The regional lymph nodes are rarely enlarged. Metastases never occur.

There are two pathologic types. One is characterized chiefly by fibrosis, and the other, chiefly by lymphocytic infiltration. These types do not include the somewhat similar-appearing pathologic changes of tuberculosis, syphilis, adenomas with fibrosis, atrophy and fibrosis of myxedema and the lymphocytic infiltration of hyperthyroidism.

It is the commonly accepted opinion that the lymphoid form represents the early, and the fibrous form the late, stage of the same disease. A study of twelve cases and a review of reported cases to date suggest that these types are probably separate and distinct entities.

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The cases which I shall record in detail were observed during eighteen hundred thyroidectomies performed at the Presbyterian Hospital. They were selected from a somewhat larger group after careful review of the clinical as well as the pathologic features. This group included cases in which the condition was thought to be "chronic thyroiditis," "tuberculosis of the thyroid (?)" and "syphilis (?)" and cases of unusual fibrosis and lymphoid hyperplasia not associated with adenoma, hypothyroidism or hyperthyroidism.

#### HISTORICAL SUMMARY

Riedel in 1883 observed a rare and peculiar condition of the thyroid gland which he described as "chronic inflammation of the gland leading to the formation of an iron-hard tumor." It was not until twelve years later that he had the opportunity to observe a second case and in the following year a third one. In 1896 and 1897, he published his observations of the disease to which he gave the name *eisenharte Struinitis*.

However, it is worthy of mention that Bowlby also observed a similar case in 1885 and reported his observations in the following year, twelve years before Riedel, under the title "Infiltrating Fibroma (? sarcoma) of the Thyroid Gland."

The condition has been subsequently described by various writers under names more or less descriptive of some of the clinical or pathologic features, namely, *inflammation chronique primitive, caucériforme*, Tailhefer, 1898; *dégénérescence fibreuse du corps thyroïde*, Ricard, 1901; primary chronic inflammation, Berry, 1901; *eisenharter Struinitis*, Silatschek, 1910; *Riedelsche Struma*, Spannus, 1910; *thyroidite ligueuse*, Delore and Alamartine, 1911; thyroiditis chronica maligna, Meyer, 1913; *chronische Thyroiditis*, Heineke, 1914; woody thyroiditis, Nicholason, 1921; chronic thyroiditis (primary), Thomas and Webb, 1923; chronic productive thyroiditis, St. George, 1924; nonsuppurative chronic thyroiditis, Hahn, 1925; benign granuloma of the thyroid, Heyd, 1929; thyroiditis simplex, Bruce, 1931.

In 1912 Hashimoto reported four cases of "chronic inflammation of the thyroid," all of which occurred in women. To this disease he gave the name struma lymphomatosa. These cases differed from those previously described in that the enlargement of the thyroid gland was due primarily to a dense infiltration of lymphoid tissue rather than being chiefly composed of fibrous tissue. He concluded this was not the same disease that had been described by Riedel and excluded his cases from those of lymphosarcoma, tuberculosis, syphilis and hyperthyroidism.

Ewing applied the name benign granuloma to this type, which he believed to be the early stage of the previously described disease. Subsequent writers, with few exceptions (Reist [1912], Heineke [1914], Perman and Wahlgren [1927] and Graham and McCullagh [1931]),



have accepted this opinion and have recorded cases similar to those described by Hashimoto as instances of an early stage of Riedel's strumitis.

#### REPORT OF CASES OF THE FIBROUS TYPE

CASE 1 (Reported by St. George).—*History*.—A Russian man, aged 25, was admitted to the hospital on Dec. 9, 1919, with the complaints of swelling of the neck, dyspnea and dysphagia of three months' duration. The family, past and personal histories were essentially unimportant. The patient had always enjoyed good health, and there was no history of previous symptoms referable to the thyroid gland. Three months before admission he first noticed a swelling on the right side of the neck, and during this period dyspnea and dysphagia developed.

*Examination*.—The temperature was 98.6 F.; the pulse rate, 98, and the respiratory rate, 20. The results of the physical examination were negative, except for obvious dyspnea and the presence of a mass the size of a hen's egg, corresponding in position to the right lobe of the thyroid gland. The Wassermann reaction, the blood count and the basal metabolic rate were not recorded.

A diagnosis of sarcoma of the thyroid gland was made.

*Operation* (Dr. George E. Brewer; December 10).—The right lobe of the thyroid gland was involved in a new growth which extended out into the surrounding tissue, causing a great increase in the density of the capsule. The recurrent laryngeal nerve was enclosed, and the gland was adherent to the trachea and the esophagus. The lower pole was well below the clavicle. The mass was very hard and but slightly movable. The overlying muscles were densely adherent, which made the exposure difficult. It was necessary to resect a portion of the clavicle to deliver the lower pole. In one area a portion of the mass invaded the wall of the trachea and could not be removed. All the remaining tumor was excised, and 120 mg. of radium was placed in the region of the portion which was left. The radium was removed two hours later.

*Pathologic Report*.—The specimen measured 3 by 4.5 by 4.5 cm. The surface was irregular and partially covered by a capsule. The tissue was stony hard. On section, there was a central portion 1.5 cm. in diameter with a similar area in one pole, which had the appearance of thyroid parenchyma containing colloid. The remaining major portion of the specimen was composed of dense, hard, white fibrous tissue.

Microscopically, the sections were almost entirely composed of dense, hyalinized, fibrous connective tissue throughout which were numerous plasma cells and scattered lymphocytes. A few scattered degenerating acini were interspersed through the sections. The zone between the fibrous area and the recognizable thyroid parenchyma was formed of dense collections of lymphocytes, in which there was only an occasional germinal center. The remaining acini contained colloid and were lined by low cuboidal epithelium. There was a marked increase in the intervening connective tissue stroma, and here also small collections of lymphocytes and scattered lymphocytes were present. No polymorphonuclear leukocytes or giant cells were noted. The acini at the inner edge of the fibrous zone showed varying degrees of degeneration. The vessels showed no evidence of pathologic change.

*Postoperative Course*.—The convalescence was uneventful except for a slight increase in dyspnea on the sixth day. Radium was applied externally on the eleventh day for four hours. The patient was discharged on the twenty-fourth

day free from symptoms. He was alive and well, free from symptoms and without evidence of recurrence thirteen and one-half years after operation.

*CASE 2.—History.*—A Japanese housewife, aged 47, was admitted to the hospital on July 19, 1928, with the complaint of swelling of the neck of one month's duration. The family history was not obtainable. The patient had always been healthy. Her husband died from an unknown cause. There were two children alive and well, and two had died in infancy. There was no history of a previous disorder of the thyroid gland. Her weight had been constant, about 135 pounds (61.2 Kg.), until four months before admission, during which time she lost 20 pounds (9.1 Kg.). She had pleurisy with effusion at the age of 18, following which she was incapacitated for about one year. Two years before admission she began to tire easily, noticed a fine tremor of the hands and experienced dyspnea on exertion. One month before admission she noticed a swelling on the left side of her neck, which increased in size. She was conscious of the mass on swallowing and experienced a throbbing sensation on the left side of the head.

*Examination.*—The temperature was 99.2 F.: the pulse rate, 100, and the respiratory rate, 20. The blood pressure was 128 systolic and 80 diastolic. The weight was 116 pounds (52.6 Kg.). The patient was well developed and well nourished. There was no exophthalmos or ocular signs associated with exophthalmic goiter. There was an asymmetrical enlargement of the thyroid gland, the left side being much larger than the right. The gland was nodular, firm and slightly tender. There was no tremor of the fingers. The basal metabolic rate was 4. Urinalysis gave negative results. The Wassermann reaction was negative. The blood count was not recorded. Because of the loss of weight, the rapid growth of the mass and the extreme hardness, the possibility of carcinoma was suspected.

A diagnosis of carcinoma of the thyroid gland was made.

*Operation* (Dr. Frank Meleney; July 23, 1928).—All the left lobe and the isthmus were involved in a hard nodular process. There seemed to be slight infiltration of the capsule at the lower pole. On the right, however, only a small portion of the gland near the isthmus seemed to be involved. Almost the entire left lobe and the isthmus were removed.

*Pathologic Report.*—The gross specimen consisted of three pieces of tissue, which measured 4 by 2.5 by 1 cm., 4 by 3 by 1.5 cm. and 3 by 1 by 1 cm., respectively. All were similar in appearance. They were very firm in consistency. The cut surface had a homogeneous dense, grayish, fibrous appearance, throughout which were scattered areas of light brown. In only a small portion of one piece could colloid be recognized. In this there appeared to be marked fibrous trabeculae extending through the colloid. No cysts or adenomas were present. The capsule was thin.

Microscopic examination showed little recognizable thyroid tissue. The sections were almost entirely composed of coarse bands and interlacing strands of dense fibrous connective tissue, for the most part hyalinized. Scattered lymphocytes and plasma cells were present, but no lymph follicles were noted. The remaining acini formed scattered groups. Some were lined by flattened epithelium and contained colloid. Others showed varying degrees of degeneration and absence of colloid. There were many giant cells in this area. These multinuclear cells had an appearance strongly suggestive of fusion of epithelial cells from the acini around droplets of colloid. No areas of necrosis, caseation or calcification were noted. An extensive search for tubercle bacilli was made in sections stained by the Ziehl-Neelsen method, but none were found.

*Postoperative Course.*—The patient regained the lost weight within two months. She was well three years after operation, was able to do all her housework and was free from symptoms.

*CASE 3.—History.*—A Mexican housewife, aged 35, was admitted to the hospital on July 31, 1929, with complaints of weakness and loss of weight of six months' duration and of swelling of the neck of eight months' duration. The family history was unimportant. The patient had always lived in Mexico and had come to New York one week before admission. There were no previous serious illnesses. She was married and had eight children, all of whom were



Fig. 1 (case 3).—A section of the thyroid gland in a case of thyroiditis (fibrous type) showing fibrous tissue throughout this peripheral portion of the gland. The acini are all small, atrophic and widely separated. There are few inflammatory cells. Magnification,  $\times 150$ .

living. Eight months before admission she first noticed a swelling in the region of the thyroid gland. This was tender at first but not at the time of admission. She lost 25 pounds (11.3 Kg.) of weight during this time and experienced dyspnea on exertion and attacks of dizziness. She also noticed a fine tremor of the hands.

*Examination.*—The temperature was 99 F.; the pulse rate, 100, and the respiratory rate, 22. The blood pressure was 160 systolic and 83 diastolic. The weight was 123 pounds (55.8 Kg.). The patient was well developed and well nourished. There was no exophthalmos. The left lobe of the thyroid gland was larger than

the right, and both were very firm. The left lobe was slightly tender. The red blood cells numbered 4,240,000, with 92 per cent hemoglobin; the white blood cells numbered 8,700, with 67 per cent polymorphonuclears, 25 per cent lymphocytes and 8 per cent eosinophils. The Wassermann reaction was negative. The basal metabolic rate was +16. The urine contained an occasional hyaline cast. The patient was given compound solution of iodine for eight days prior to operation.

A diagnosis of adenoma of the thyroid gland was made.

*Operation* (Dr. W. B. Parsons; August 13).—The gland was small, firm and sclerotic. The overlying muscles were adherent to the upper pole. The capsule

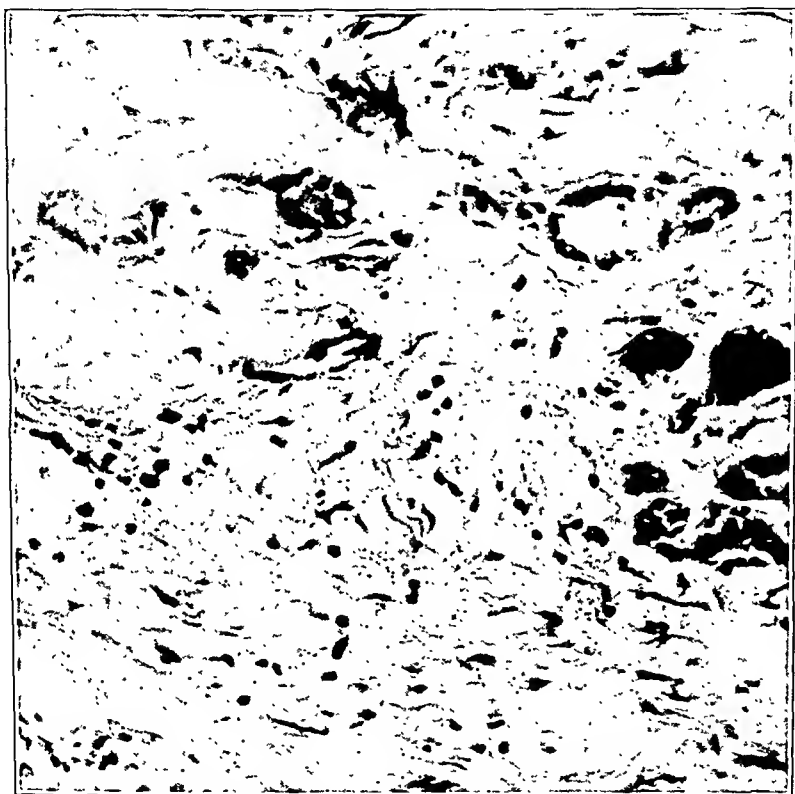


Fig. 2 (case 3).—A high magnification of the section shown in figure 1. Atrophic thyroid acini are seen scattered through the dense fibrous tissue. Magnification,  $\times 500$ .

was very thick. The gland appeared to be made up of fibrous tissue in which there were a few small areas of thyroid parenchyma. The left lobe was somewhat larger than the right. A subtotal resection was done on both sides.

*Pathologic Report.*—The gross specimen consisted of portions of both lobes of the thyroid gland. These measured 4 by 2 by 1 cm. and 3 by 1.5 by 0.4 cm., respectively. The appearance was similar. The outer surface was rough. The cut surface showed numerous fibrous septums running throughout, with intervening pink areas.

Microscopically, there was a marked increase in the interlobular and intra-lobular stroma formed of dense connective tissue showing a mild degree of hyalinization. The acini were small and formed groups which were widely separated by dense connective tissue (fig. 1). They were lined by cuboidal epithelium, and very few contained colloid. Many appeared compressed and seemed to be undergoing degeneration (fig. 2). An occasional giant cell was present. A small collection of lymphocytes and many scattered lymphocytes were present in the stroma. There were no germinal centers. There were no polymorphonuclear leukocytes, but many plasma cells were present. The vessels were not thickened. No tubercles, areas of caseation or adenomas were noted.

*Postoperative Course.*—The patient was discharged on the fourteenth day. She returned to Mexico and still suffered from several of her preoperative symptoms, especially fatigue, with the addition of palpitation. Six months after operation she noticed a swelling on the right side of the neck in the region of the thyroid gland. There was, however, no dyspnea, dysphagia or cough. The swelling was slightly painful. The patient had lost 16 pounds (7.3 Kg.) in weight. The basal metabolic rate was +8. The blood pressure was 200 systolic and 120 diastolic. It seems certain from recent examination of the patient, two years after operation, that many of the initial symptoms were due not to hyperthyroidism but rather to hypertension and chronic nephritis, which was confirmed by laboratory examinations.

*CASE 4.—History.*—A Negress, aged 42, was admitted to the hospital on Dec. 23, 1929, with the complaint of a lump in the neck of three months' duration. The family history was unimportant. There had been no serious illnesses, and there was no history of recent infections, of previous symptoms referable to the thyroid gland or of venereal disease. Three months before admission the patient noticed a slight swelling of the neck. This increased slowly at first but enlarged rapidly in the three weeks before admission. The mass was not tender. There was slight hoarseness, which the patient attributed to a cold, but no dyspnea, dysphagia, palpitation, nervousness or loss of weight.

*Examination.*—The temperature was 99 F.; the pulse rate, 90, and the respiratory rate, 20. The blood pressure was 124 systolic and 90 diastolic, and the weight was 147 pounds (66.7 Kg.). The patient was well developed and well nourished. No tremor or exophthalmos was present. There was a moderate-sized, firm, nontender movable mass in the left lobe of the thyroid gland. The right lobe was smaller and irregular. The regional lymph nodes were not enlarged. The Wassermann reaction was 4 plus. The basal metabolic rate was  $\pm 0$ . The urine was normal. A roentgenogram showed a possible substernal prolongation of the mass, with a slight deviation of the trachea to the right. Because the mass did not feel like an adenoma and was slightly more fixed than usual, syphilis of the thyroid gland was considered as a possible diagnosis. Three intravenous injections of neoarsphenamine were given at weekly intervals. As there was no change in the mass, operation was decided on.

A diagnosis of adenoma of the thyroid gland and syphilis of the thyroid gland (?) was made.

*Operation* (Dr. L. Sloan; December 26).—The thyroid gland on the left side was very hard, and practically the entire lobe seemed to be involved in a sclerosing process, which involved not only the gland itself but also the structures adjacent to it. The under-surfaces of the pretracheal muscles and the tissue over the greater vessels were adherent to the thyroid gland, and were formed of tissue which resembled the wall of a long-standing abscess, but not a gumma. It was

possible only with great difficulty to separate the thyroid gland from the adjacent structures because of adhesions and the resistance of the tissue. Toward the left upper pole and midline at the lower pole the resistant tissue seemed to merge into normal-appearing gland. On the right side there were two or three small nodules, but the process seemed to be different from the left side. There was a pyramidal lobe which appeared to be free from pathologic change. Both lobes extended behind the sternum. The trachea was considerably displaced to the right. The entire left lobe, the pyramidal lobe and a portion of the right lobe were removed.

*Pathologic Report.*—The gross specimen consisted of portions of both lobes of the thyroid gland. These measured 7 by 6 by 4.5 cm. and 6 by 3 by 2.5 cm. The larger was somewhat cylindric, and one surface was almost entirely covered by a thin fibrous capsule. The specimen felt quite firm. On section, the surface presented a dense, thick, white peripheral portion almost entirely surrounding a zone of what appeared to be thyroid tissue. A small layer of thyroid tissue formed the outer edge. The central portion was somewhat cystic and contained areas of hemorrhage. Small areas of relatively normal-appearing thyroid tissue were present in the fibrous layers. The smaller specimen had a slightly nodular surface and was almost entirely covered by a thin fibrous capsule. It was firm throughout, but not as hard as the larger specimen. The cut surface was composed of several small areas of thyroid parenchyma separated by dense fibrous tissue. There were a few small cystlike spaces filled with colloid, but no evidence of calcification.

Microscopic section of the dense white zone showed it to be composed of hyalinized connective tissue throughout which were many plasma cells, lymphocytes and an occasional giant cell. A few degenerating acini and an occasional intact one containing colloid were present in this area. Small collections of lymphocytes occupied the intervening area between the fibrous zone and the thyroid parenchyma. These did not contain germinal centers. The acini occupying the central portion varied in size and shape. They were lined by flattened cuboidal epithelium and were well filled with colloid. Bands of coarse fibrous tissue traversed this area between groups of acini, and those at the edge showed degeneration. A few giant cells were present. These appeared to be formed by fusion of epithelial cells around colloid. There were no tubercles present. The section of the smaller lobe was similarly composed of dense hyalinized connective tissue, infiltrated with plasma cells and lymphocytes. An occasional germinal center was present. There were small groups of compressed acini scattered through the sections. These were lined with flattened epithelium and contained colloid. There were no tubercles or areas of necrosis. No tubercle bacilli were found in sections stained by the Ziehl-Neelsen method. There was nothing in the sections on which a diagnosis of syphilis could be based. The vessels were not thickened, and there was no perivascular small round cell infiltration.

*Postoperative Course.*—The postoperative convalescence was uneventful aside from a slight superficial infection of the wound. The patient was discharged on the sixteenth day and felt quite well in one month, during which there was a gain in weight and strength. There was no dyspnea, dysphagia or evidence of recurrence. The treatment for syphilis was continued. All the induration in the neck disappeared in six months. Thirteen months after operation the patient felt very well and was working without fatigue or disability. The basal metabolic rate was +3. Nineteen months after operation the patient weighed 151 pounds (68.5 Kg.). The basal metabolic rate at this time was +3. Two years after

operation she weighed 157 pounds (71.2 Kg.). There was no evidence of hyperthyroidism or hypothyroidism and no evidence of recurrence. The Wassermann reaction was negative.

*CASE 5.—History.*—A woman, aged 60, was admitted to the hospital on Aug. 14, 1931, with the complaint of a swelling of the neck of two months' duration. The family history was irrelevant. The patient was born in Poland but had lived in the United States for twenty-seven years. She had been married thirty-five years and had five children, all of whom were alive and well. There was no history of a previous disorder of the thyroid gland or of serious illnesses. Three months before admission the patient thought that she had caught a cold, and she awoke one morning with stiffness of the neck. About one month later she noticed a swelling of the neck. This did not increase in size up to the time of admission. There was no pain, but slight tenderness on pressure was experienced. There was no nervousness, palpitation, tremor, exophthalmos, dyspnea, dysphagia or aphonia.

*Examination.*—The temperature was 99.8 F.; the pulse rate, 74, and the respiratory rate, 20. The blood pressure was 160 systolic and 104 diastolic, and the weight was 125 pounds (56.7 Kg.). The patient was well developed and well nourished. There was a marked enlargement of the thyroid gland in the anterior aspect of the neck. This was extremely hard. It moved on swallowing and was not attached to the skin. The mass was slightly tender on pressure. The surface was smooth. There were several small firm nodes in both submaxillary regions. There was no exophthalmos or tremor. The lungs were clear. A roentgenogram of the neck showed calcification of the left side, with some deviation of the trachea to the right. Because of the extreme hardness of the gland, carcinoma with metastases was suspected. One node, removed for biopsy, proved on microscopic examination to be tuberculous. The Wassermann reaction was negative. The basal metabolic rate and the blood count were not recorded.

A diagnosis of carcinoma and tuberculosis (?) of the thyroid gland was made.

*Operation* (Dr. L. Sloan; August 31).—The gland was extremely hard and considerably enlarged, but there was no evidence of invasion of the surrounding tissue. It was not adherent to the muscles and stripped away from the trachea with ease. The appearance was homogeneous throughout and was that of an encapsulated gland with very dense and fibrous parenchyma, which in some areas resembled normal thyroid. The left lobe was twice the size of the right. Almost a perfect mold of the trachea was formed on the posterior surface. The major portions of both lobes with the entire isthmus were removed. There was little bleeding.

*Pathologic Report.*—The specimen consisted of the major portions of both lobes of the thyroid gland and the isthmus. Both lobes were almost entirely covered by a thin smooth capsule. The right portion measured 7 by 4.5 by 2.5 cm. The surface was finely irregular but not nodular. The left measured 9 by 6.5 by 4.5 cm. This was grossly lobulated. Both were similar on section. They were extremely dense and cut with increased resistance. The appearance was that of homogeneous dense white fibrous tissue, with little evidence of colloid. There were no adenomas or areas of calcification.

Microscopically, sections from different portions of both specimens were similar. They showed many coarse bands of hyalinized connective tissue arranged in a very irregular manner. The intervening spaces were formed of interlacing strands of dense connective tissue, which was also for the most part hyalinized. The

intervening spaces between the strands of connective tissue contained numerous plasma cells and lymphocytes. Little parenchyma remained. Very few acini exhibiting various degrees of degeneration were scattered through the sections. An occasional one contained colloid. These showed no evidence of epithelial hyperplasia. A few multinucleated giant cells were present which had the appearance of being formed by fusion of epithelial cells around droplets of colloid. No pathologic changes were noted in the vessels. The lymphocytes for the most part were diffusely scattered, with the exception of a few small collections, only one of which contained a germinal center. There were no tubercles present.

*Postoperative Course.*—The patient was discharged on the fourteenth day. She was slightly hoarse two months after operation. The basal metabolic rate was 10. Laryngoscopic examination showed paralysis of the left vocal cord. The patient was given thyroid extract, 0.03 Gm., three times a day. One month later she was feeling stronger and doing housework without fatigue. There was still some hoarseness present. The basal metabolic rate was 8. Nine months after operation there was no evidence of myxedema; consequently the administration of thyroid extract was discontinued. The basal metabolic rate was 3. The patient was well and was free from symptoms and evidence of myxedema fifteen months after operation. Six months later her general appearance was good, and the skin was warm and soft and not thick. She had become more obese, but the obesity was not of an abnormal type. She looked less like a person with hypothyroidism than before operation. Thyroid extract, 0.06 Gm. daily, was prescribed. Two years after operation the patient weighed 155 pounds (70.3 Kg.). Her general health was excellent, and no evidence of hypothyroidism was noted. There was no evidence of recurrence.

*CASE 6.—History.*—A Jewess, aged 31, was admitted to the hospital with complaints of swelling of the neck of eighteen months' duration and dysphagia of four months' duration. The family history was unimportant. There was no history of previous serious illnesses or of disorders of the thyroid gland. She had been previously treated with a diet for a gastric ulcer, the presence of which had been confirmed by roentgenographic examination. She was free from symptoms for five years. Eighteen months before admission she noticed a swelling of the neck. There was no fatigue, nervousness, loss of weight, tremor or irritability. The basal metabolic rate on a previous examination was "normal." The swelling increased markedly in the four months prior to admission. The patient experienced a sense of fullness in the neck, with dysphagia but no dyspnea, pain or palpitation.

*Examination.*—The temperature was 99 F.; the pulse rate, 88, and the respiratory rate, 22. The blood pressure was 143 systolic and 75 diastolic. The weight was 140 pounds (63.5 Kg.). The patient was a well developed and well nourished woman who did not appear to be acutely ill. There was no exophthalmos. There was a diffuse, stony hard swelling of the thyroid gland which was not tender and moved on swallowing. The lateral lobes and the isthmus were clearly defined. The skin was freely movable, and the gland did not feel attached to the deeper structures. The regional lymph nodes were not enlarged. The urine was normal. The blood count and Wassermann reaction were not recorded.

A diagnosis of chronic thyroiditis was made.

*Operation.* (Dr. W. B. Parsons; March 9).—The thyroid gland was hard; the normal gland had been apparently replaced by dense white tissue. There was no apparent invasion of the overlying structures. A frozen section showed what



was thought to be a malignant condition of the thyroid gland, and consequently total thyroidectomy was performed. The parathyroid bodies were carefully preserved.

*Pathologic Report.*—The specimen consisted of the entire thyroid gland. This was in three pieces, which measured 7 by 4 by 2.5 cm., 6 by 4.5 by 2.3 cm. and 4 by 2.2 by 1.5 cm., respectively. They were irregular in shape, and the surfaces were coarsely nodular. Each was stony hard in consistency and cut with difficulty. They were similar on section, being composed of dense white fibrous

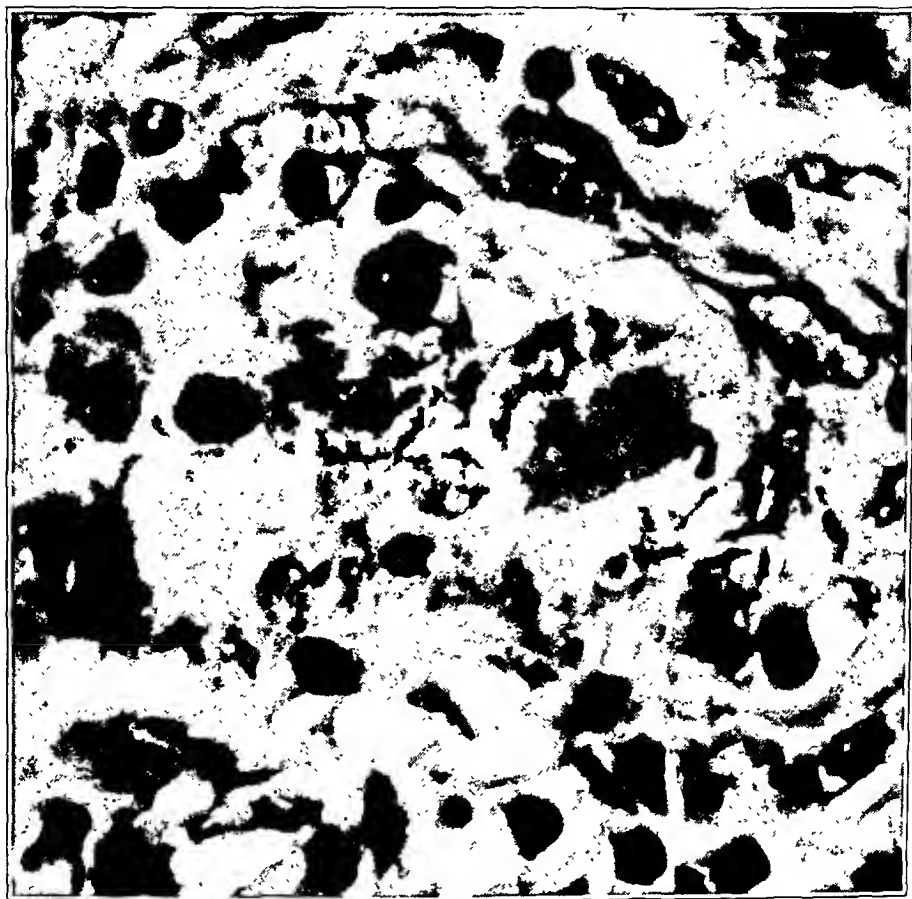


Fig. 3 (case 6).—A high power detail photomicrograph of a section of the thyroid gland in a case of thyroiditis (fibrous type) to show the type of cellular infiltration. The majority of the small cells with eccentric nuclei are plasma cells. The lymphocytes are the small cells with darkly stained, centrally placed nuclei. The larger cells toward the center of the picture with granular cytoplasm are thyroid epithelial cells. They have lost their acinar arrangement. Thick bands of collagen are seen in all parts of the picture. Magnification,  $\times 700$ .

tissue. There was no recognizable thyroid tissue present. No areas of degeneration or of calcification were observed.

Microscopically, there was a diffuse formation of hyalinized fibrous connective tissue. This was arranged in the form of dense bands with intervening areas of interlacing strands of connective tissue. The acini were separated by connective

tissue and appeared compressed. Few contained colloid, and many showed degeneration. Numerous multinuclear giant cells were present, formed by fusion of epithelial cells of the acini. Some contained droplets of colloid. The epithelium was cuboidal. Many plasma cells and lymphocytes were scattered through the fibrous tissue (fig. 3). A few small collections of lymphocytes were present. These were most marked in the thickened capsule. The vessels showed no unusual change. No tubercles or areas of necrosis were noted. There was no evidence of malignancy.

*Postoperative Course.*—The basal metabolic rate on the fifth day was  $-7$ . The patient was discharged on the tenth day. Two weeks after operation she complained of a peculiar sensation in her hands. A Chvostek sign which had been present a week before could not be elicited. Calcium chloride was prescribed. Five months later the patient weighed 127 pounds (57.6 Kg.). The basal metabolic rate was  $+14$ . There was no evidence of deficiency of calcium metabolism or hypothyroidism. Nine months after operation she showed signs of myxedema for the first time. The weight was 132 pounds (59.9 Kg.). The speech was thick, and there was puffiness under the eyes. The basal metabolic rate was 7. Thyroid extract, 0.06 Gm. three times a day, was prescribed.

*CASE 7.—History.*—A Puerto Rican woman, aged 38, was admitted to the hospital on Dec. 4, 1931, with complaints of soreness of the throat and a swelling of the neck of one month's duration and chills, fever and dysphagia of four days' duration. The family history was unimportant. The patient was married and had two children, who were alive and well. There had been no serious infections or previous symptoms referable to the thyroid gland. For one month before admission she had noticed pain on pressure in the region of the thyroid gland and a slight swelling. This slowly increased in size until four days before admission, when the patient experienced difficulty and pain on swallowing. At this time she had a chill in the evening and one each of the following evenings, with a feeling of fever afterward, which she attributed to a cold.

*Examination.*—The temperature was 99.8 F.; the pulse rate, 84, and the respiratory rate, 20. The blood pressure was 114 systolic and 82 diastolic, and the weight was 131 pounds (59.4 Kg.). The patient was well developed and well nourished and did not appear to be acutely ill. There was no exophthalmos or evidence of hyperthyroidism or hypothyroidism. There was a slight fulness of the left side of the neck in the region of the thyroid gland. A few small slightly tender lymph nodes were present on each side of the neck. There was marked tenderness over the left lobe of the thyroid and the isthmus. This felt firm. The overlying skin was not indurated or adherent, nor was the gland adherent to the surrounding structures. No fluctuation was present. The blood count on admission was 14,500 white blood cells, with 67 per cent polymorphonuclears, 29 per cent lymphocytes, 3 per cent monocytes and 7 per cent eosinophils. Two days later the count was 3,420,000 red blood cells, with 70 per cent hemoglobin and 10,240 white blood cells with 70 per cent polymorphonuclears, 27 per cent lymphocytes, 2 per cent monocytes and 1 per cent eosinophils. The basal metabolic rate was  $+33$ . This, however, was not considered a true reading because of fever and poor cooperation of the patient. The Wassermann reaction was negative. Urinalysis and laryngoscopic examination gave negative results. An ice collar was applied to the neck for three days before operation, at which time the temperature varied between 99.2 and 101.8 F.

A diagnosis of chronic thyroiditis was made.

*Operation* (Dr. L. Sloan; December 8).—The left lobe was very hard and seemed to be made up of fibrous tissue similar to that of the previous glands, which was described as presenting chronic thyroiditis. The left lobe was larger than the right, but even so it was quite small. The gland was adherent to the surrounding structures, but not so much so that it could not be stripped away. It was closely adherent to the trachea. The capsule appeared thickened. The right lobe was softer than the left, but there was not a sharp line between the soft portion and that which was stony hard. The major portion of both lobes and the isthmus were removed.

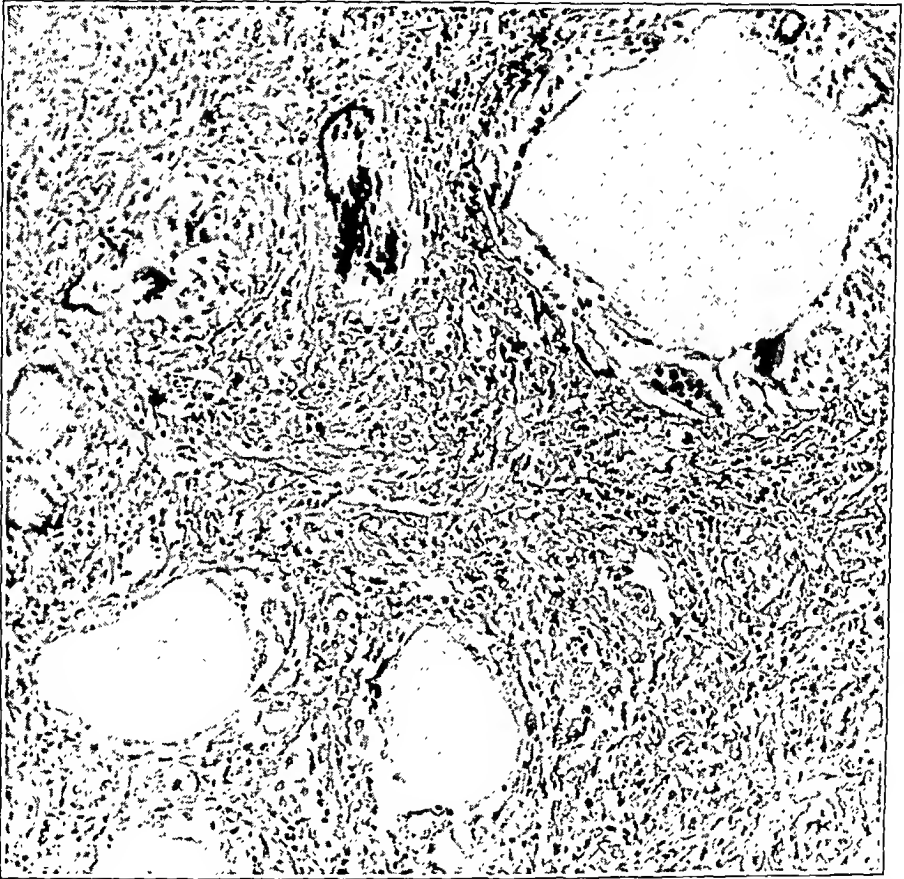


Fig. 4 (case 7).—A section of the thyroid gland in a case of thyroiditis (fibrous type). In this case the fibrosis is associated both with an inflammatory cell infiltration and with acinar destruction with phagocytosis of the colloid by multinucleated giant cells. This sometimes gives cell groupings resembling tubercles. Magnification,  $\times 150$ .

*Pathologic Report.*—The specimen from the left lobe with the isthmus measured 4 by 2 by 1.2 cm. One surface, coarsely irregular, was covered by a thin capsule to which strands of connective tissue were adherent, suggesting adhesions. The tissue was very firm and cut with increased resistance. The cut surface showed coarse white fibrous trabeculae with intervening yellowish-pink areas. There was no recognizable colloid. No adenomas or areas of calcification were noted. The portion from the right lobe measured 3.5 by 2 by 0.8 cm. The major portion

of the capsule was covered with adherent fibrous tissue and a small portion of muscle. On section, this lobe was more densely fibrous than the left.

Microscopically, sections of the two lobes were essentially similar. The small amount of remaining thyroid parenchyma was represented by a few scattered acini lined by low cuboidal epithelium, for the most part poorly filled with colloid (fig. 4). The intervening areas were formed of dense fibrous tissue in which

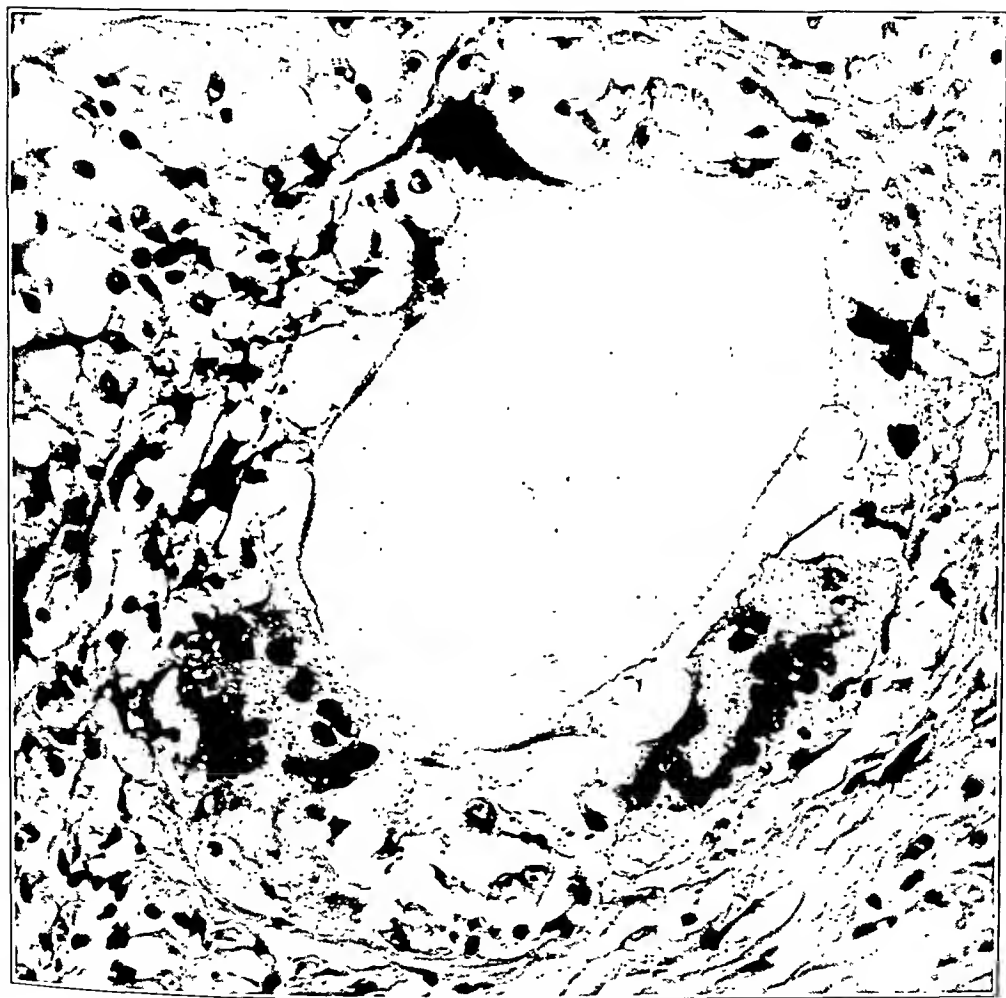


Fig. 5 (case 7).—A section of the thyroid gland in a case of thyroiditis (fibrous type) showing an acinus with complete disappearance of recognizable acinar cells and persistence of colloid and surrounding the latter syncytial multinucleated aggregates which are probably phagocytes. At the left is a vacuolated remnant of colloid. Lymphocytes and plasma cells are seen throughout the picture. Magnification,  $\times 909$ .

there were many large multinuclear giant cells containing droplets of colloid. These had the appearance of being formed by fusion of several epithelial cells (fig. 5). There was extensive degeneration of the acini without hyperplasia of

the remaining ones. Many lymphocytes, plasma cells and polymorphonuclear leucocytes were present throughout the sections. No areas of necrosis or suppuration were noted. The fibrous and lymphocytic infiltration extended beyond the capsule into the surrounding muscle and fat. An adherent lymph node exhibited several hyperplastic germinal centers. Several large arteries outside the capsule showed calcification of the inner portion of the media. Tissue from the gland was injected into guinea-pigs, which at autopsy showed no evidence of tuberculosis.

*Postoperative Course.*—The temperature became normal on the third day and remained so. The patient was discharged on the eleventh day. The basal metabolic rate was  $-11$ . Six months after operation the weight was 139 pounds (63 Kg.); the pulse rate, 72, and the basal metabolic rate,  $-30$ . The patient felt tired and listless. The skin was not thickened. There was no loss of hair. Thyroid extract was prescribed. Two months later the patient was admitted to another hospital, unconscious. She remained five days and left against advice. The nature of the attack was unknown. There were no complaints. The pulse was regular; there were no signs of hypothyroidism, and the basal metabolic rate was  $-18$ . The basal metabolic rate one year after operation was  $-22$ . The patient did not have the appearance of a person with hypothyroidism. There was no evidence of recurrence.

**CASE 8.**—*History.*—A married Negress, aged 43, was admitted to the hospital on July 8, 1931, with complaints of swelling of the neck of five years' duration, a loss of 25 pounds (11.3 Kg.) in weight in the previous year and nervousness of six months' duration. The family history was unimportant. The patient was born in British Guiana and had lived in the United States eight years. There was no history of a previous disorder of the thyroid gland. She had one child alive and well and had had no miscarriages. She had malaria from eight to ten years before admission and pleurisy three years before. She had enjoyed good health until the previous year, when she began to lose weight and noticed increasing nervousness. A mass had been present in the neck for five years. There was no pain, dyspnea or dysphagia.

*Examination.*—The temperature was 99 F.; the pulse rate, 82, and the respiratory rate, 20. The blood pressure was 155 systolic and 105 diastolic, and the weight was 124 pounds (56.2 Kg.). The patient was well developed and well nourished. There was no exophthalmos. The thyroid gland was easily palpable. It was firm, moderately enlarged and freely movable. There was no tremor or dyspnea, though slight tachycardia was noted. The regional lymph nodes were not enlarged. Because of the firmness of the gland, calcification of an adenoma was considered and also carcinoma and Riedel's strumitis. The basal metabolic rate was  $+12$ ; the test for sugar in the urine gave a 4 plus reaction; the blood sugar content was 3.06 Gm. per liter. The red blood cells numbered 4,240,000, with 85 per cent hemoglobin; the white blood cells numbered 6,600, with 65 per cent polymorphonuclears, 33 per cent lymphocytes and 2 per cent monocytes. The Wassermann reaction was not recorded.

A diagnosis of adenoma of the thyroid gland (nontoxic), carcinoma (?), Riedel's strumitis (?) and diabetes mellitus was made.

*Operation* (Dr. W. B. Parsons; July 11).—The gland was symmetrically enlarged, particularly in the anterior direction, and was firm and white and felt calcified. The cut surface showed several raised circumscribed areas. A frozen section was made, and although a definite diagnosis could not be established it was thought that the condition was chronic thyroiditis rather than a malignant growth. The gland was not adherent. Half of the right lobe was removed.

*Pathologic Report.*—The specimen consisted of a portion of one lobe of the thyroid gland. It measured 3.5 by 2.5 by 2 cm. Two thirds of the surface was covered by a thin capsule. The gland was extremely firm but not stony hard. The cut surface was smooth and of a homogeneous pale grayish color. There were no areas of hemorrhage, degeneration, adenomas or calcification. The appearance and consistency were not those of carcinoma.

Microscopically, the sections showed a marked increase in fibrous connective tissue. For the most part this was hyalinized and formed coarse bands with inter-

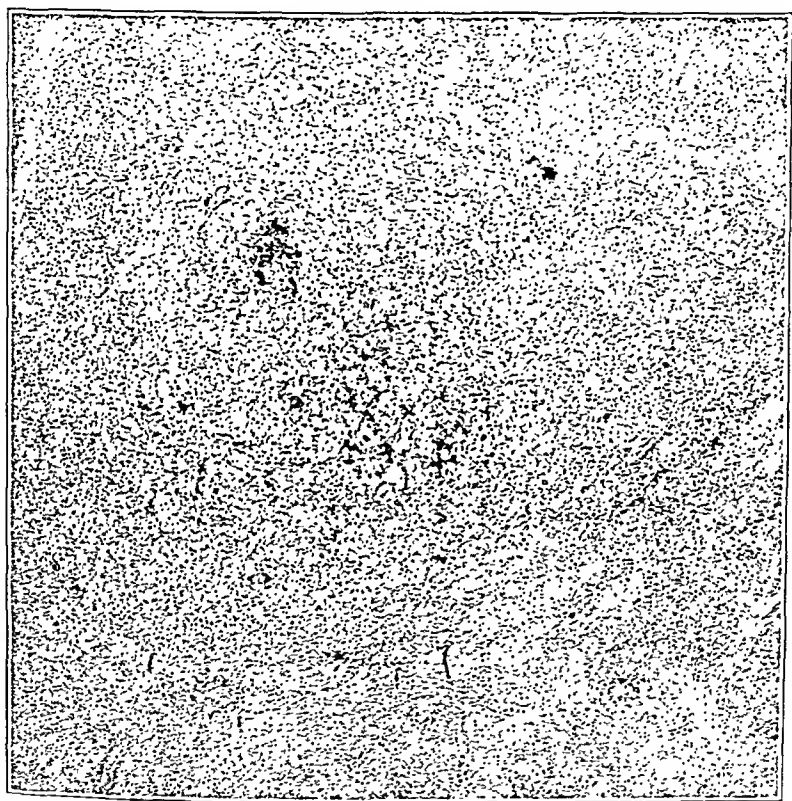


Fig. 6 (case 8).—A section of the thyroid gland in a case of thyroiditis (fibrous with lymphoid infiltration). There is marked generalized fibrosis, with atrophy of acini and reduction in colloid and also a generalized lymphocytic and plasma cell infiltration, with the formation of occasional lymph follicles. Magnification,  $\times 100$ .

vening strands. Numerous lymphocytes and plasma cells were present in the spaces. A few lymph follicles with hyperplastic germinal centers were noted (fig. 6). The acini were small and widely separated. Very little colloid was evident. The epithelial cells were cuboidal and pale-staining and did not show evidence of hyperplasia. Some of the acini were undergoing degeneration. A few giant cells were present, apparently formed of fused epithelial cells about droplets of colloid. There was nothing suggestive of tuberculosis, syphilis or a malignant condition.

*Postoperative Course.*—The patient was discharged on the sixth day and had fully recovered in four months. There were no symptoms of hyperthyroidism or hypothyroidism. The weight was 137 pounds (62.1 Kg.). The basal metabolic rate at six months was  $-4$ . There was slight hypertrophy of the remnant on the left side ten months after operation. The basal metabolic rate was  $+7$ . The patient was in excellent health twenty-seven months after operation. The weight was 137  $\frac{1}{2}$  pounds (62.3 Kg.). The right lobe was now firm and rounded and was similar in appearance to that before operation.

*CASE 9.—History.*—A woman, aged 49, was admitted to the hospital on Nov. 13, 1931, with the complaint of a lump in the right side of the neck, with pain of three weeks' duration. The family history was unimportant. The patient was born in Czecho-Slovakia but had lived in the United States for twenty-four years. She was married and had four children alive and well. There was no history relative to a previous disorder of the thyroid gland. The patient had enjoyed good health until five months before admission, at which time she first noticed that she was losing weight and strength and perspired profusely. These symptoms were of a mild nature until three weeks before admission, when she experienced pain at the angle of the jaw, which radiated to the right ear. She noticed a firm lump about the size of a walnut in the right side of the neck. A dry cough developed. There was no palpitation, dyspnea or dysphagia. She lost 15 pounds (6.81 Kg.) in weight in the previous three months.

*Examination.*—The temperature was 98 F.; the pulse rate, 88, and the respiratory rate, 20. The blood pressure was 140 systolic and 80 diastolic, and the weight was 127 pounds (57.6 Kg.). The patient was well developed and well nourished. There was a tender, firm swelling in the right lobe and the isthmus of the thyroid. The swelling moved on swallowing and was not attached to the skin or the deeper structures. The left lobe was slightly enlarged. There was no exophthalmos or tremor. Roentgenograms of the chest and skeleton were normal. The urine was normal and the Wassermann reaction was negative. The basal metabolic rate was  $+14$ . The red blood cells numbered 4,070,000, with 70 per cent hemoglobin; the white blood cells numbered 7,200, with 74 per cent polymorphonuclears, 20 per cent lymphocytes and 6 per cent monocytes. Because of the hardness of the mass, carcinoma was suspected, although Riedel's strumitis was also considered. A diagnosis of carcinoma of the thyroid was made.

*Operation.* (Dr. L. Sloan; November 21).—The right lobe was unusually firm. The cut surface was dense white and homogeneous, resembling fibrous tissue. There were a few firm nodular areas on the surface with intervening softer areas. The left lobe was similar but smaller. A mold of the trachea was formed on the posterior surface of the gland.

*Pathologic Report.*—The specimen consisted of a portion of both lobes of the thyroid and the isthmus. These measured 7 by 4 by 2.5 cm. and 5 by 3 by 2 cm., respectively. Both were partially covered by a thin capsule which was torn in places. Both were similar in section. The tissue was firm and white, with areas of apparent thyroid parenchyma containing colloid. No adenomas were noted.

Microscopically, the sections showed great variation. In some areas there was a marked lymphocytic infiltration, with localized small follicles containing hyperplastic germinal centers. These sections contained very little fibrous tissue. The acini contained colloid and appeared compressed; some were degenerating. Other areas were composed chiefly of dense interlacing bands of hyalinized fibrous connective tissue, through which many lymphocytes were scattered. The acini in these areas showed varying degrees of degeneration and contained very little

colloid. Many multinuclear giant cells were present. These were formed apparently by fusion of epithelial cells and contained droplets of colloid. The epithelium was of the low cuboidal type and showed no hyperplasia. The areas which were largely fibrous were beneath the capsule, while the deeper areas were largely lymphoid. The sections were of unusual interest because they showed the two types of reaction previously not seen in one specimen. Fibrosis, however, predominated. No tubercles were present. An extensive search was made for tubercle bacilli in sections stained by the Ziehl-Neelsen method but none were found. The basal metabolic rate was  $-4$  on the day of discharge, the seventh day.

*Postoperative Course.*—The patient felt well in one month and weighed 131 pounds (59.4 Kg.). The basal metabolic rate was  $-16$ . Two months later she had definite signs of hypothyroidism verging on myxedema. The skin was dry, the eyes puffy, the hair dry, the color pale and speech slow. The weight was 147 pounds (66.7 Kg.). The basal metabolic rate was  $-29$ . The patient was given thyroid extract. Five months after operation she felt well. The basal metabolic rate was  $-15$ , and she weighed 144 pounds (65.3 Kg.). When seen nine months after operation she was taking 5 grains (0.32 Gm.) of thyroid extract a day. The basal metabolic rate was  $-6$ . There were no signs of myxedema. The patient discontinued the thyroid extract without advice. When she was seen after eighteen months her weight was 153 pounds (61.2 Kg.) and signs of myxedema had returned. Her condition improved on medication with thyroid extract, and she was free from symptoms three months later. When last seen twenty-five months after operation she again showed signs of myxedema because of failure to continue treatment. There was no evidence of recurrence of the growth.

#### REPORT OF CASES OF THE LYMPHOID TYPE (HASHIMOTO)

*CASE 10.—History.*—A nurse, aged 26, was admitted to the hospital on Dec. 14, 1922, with the complaint of swelling of the neck of seven years' duration. Her father had died of pulmonary tuberculosis. She had enjoyed good health until six years before admission, at which time she suffered from bilateral dry pleurisy. Four years later she had an attack of jaundice, which lasted one month. During the year preceding admission she had frequent attacks of indigestion at night, with nausea, headaches and vomiting of bile-colored fluid, but no blood. These attacks lasted one day; they were not relieved by medication and frequently followed a heavy meal. The patient lost 14 pounds (6.4 Kg.) in weight during this period. Seven years before admission she first noticed swelling of the neck. This slowly increased in size without giving rise to symptoms for six years, following which she experienced a feeling of constriction in the neck, most marked when she was recumbent. This was accompanied six months later by palpitation, general muscular weakness and nervousness. During the months prior to hospitalization she noticed dyspnea and for two weeks intermittent pain along the posterior borders of the sternocleidomastoid muscles and across the neck in the region of the isthmus.

*Examination.*—The temperature was 99 F.; the pulse rate, 90, and the respiratory rate, 18. The blood pressure was 120 systolic and 80 diastolic. The weight was  $123\frac{1}{2}$  pounds (56 Kg.). The patient was well developed and well nourished and not acutely ill. There were no abnormal ocular signs. The thyroid gland was diffusely enlarged and extended beneath the sternocleidomastoid muscles. The isthmus was also enlarged. The swelling was firm in consistency and most marked on the right side. There was retraction of the wall of the chest in both



the supraclavicular and the infraclavicular region. A few persistent fine râles were heard at the apex of the left lung, in the left axillary region and at the bases of both lungs. Urinalysis gave negative results. The Wassermann reaction was negative. The basal metabolic rate was  $-5$ . Roentgenograms showed extensive calcification of both hilar regions and diaphragmatic adhesions suggestive of old tuberculosis.

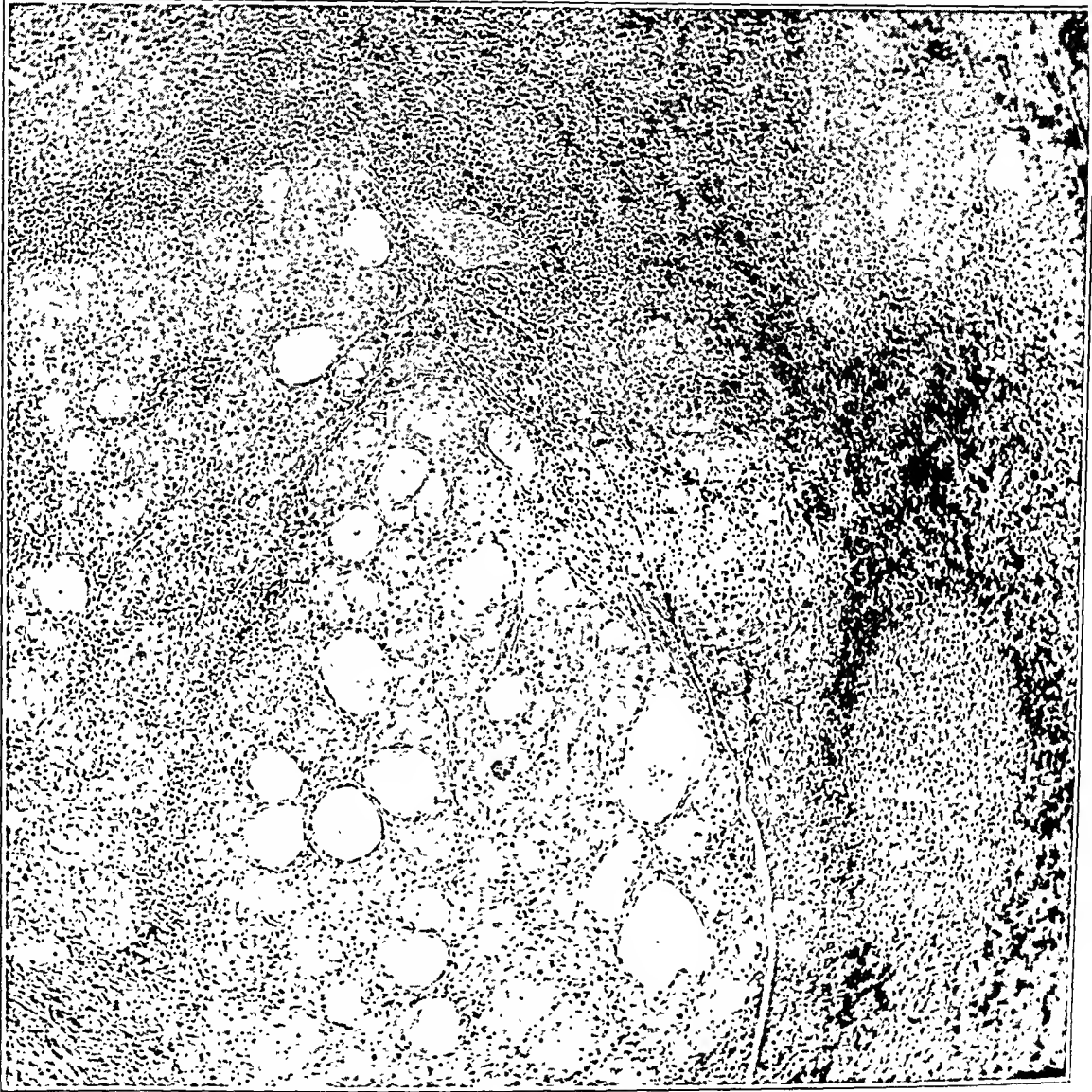


Fig. 7 (case 10).—A section of the thyroid gland in a case of thyroiditis (lymphoid type) showing numerous lymph follicles, lymphoid cell infiltration between the acini and apparent atrophy of acini with reduction of the colloid content. Magnification,  $\times 227$ .

The patient was given 0.1 Gm. of sodium iodide a day by mouth for five weeks without any noticeable change in the mass.

A diagnosis of adenoma of the thyroid was made.

*Operation* (Dr. W. B. Parsons, December 16).—There was a moderate-sized diffuse enlargement of the right lobe of the thyroid gland, which felt like an adenoma but could not be easily enucleated. The major portion was removed. Bleeding was so profuse that packing was necessary to control it.

*Pathologic Report*.—The gross specimen consisted of four irregular pieces of tissue, the largest measuring 5 by 4 by 1 cm. and the others less than 2 cm. in diameter. They were composed in part of elastic pink tissue having the appearance of pancreas. In other areas they were of dense white tissue. On section they presented irregular pink areas and a few rather dense white areas. There were no cysts or colloid.

Microscopically, the sections of each portion were similar. There was an increase in the interlobular and intralobular connective tissue. This was densely and diffusely infiltrated with lymphocytes, which formed many large and small follicles containing hyperplastic germinal centers showing occasional mitotic figures. Scattered small groups of acini were seen. These were greatly distorted and appeared compressed. Very few were lined with cuboidal cells; most, however, were lined with small atrophic cells. The lumens of many were filled with large, swollen, pale epithelial cells. Very little colloid was present (fig. 7). No giant cells were seen. There were no areas of necrosis, suppuration or areas suggestive of tubercles. The blood vessels were free from pathologic change.

*Postoperative Course*.—The recovery was prolonged by an infected hematoma in the incision. The patient was discharged on the twenty-fourth day. She gained 9 pounds (4.1 Kg.) in three months and noticed a marked improvement in her nervousness. She was admitted to another hospital fifteen months after operation, where she died following an operation for duodenal ulcer. She had no symptoms relative to the thyroid gland at this time.

*CASE 11.—History*.—A Jewess, aged 36, was admitted to the hospital on June 7, 1931, with the complaint of swelling of the neck of six months' duration. Her mother stated that she had had a slight swelling since puberty. The family history was unimportant. The patient was married; her husband and three children were alive and well. Four years before admission she was treated for a gastric ulcer with diet, which relieved the symptoms. Six months before her visit to the hospital she noticed a swelling in the midline of the neck. Two months later both sides became enlarged, and she experienced nervousness, palpitation at night, pain on the right side of the neck, attacks of choking and insomnia. There were no previous symptoms referable to the thyroid gland.

*Examination*.—The temperature was 99.6 F.; the pulse rate, 78, and the respiratory rate, 18. The blood pressure was 135 systolic and 95 diastolic. The weight was 172 pounds (78 Kg.). The patient was well developed and obese. There was no exophthalmos or ocular signs of hyperthyroidism. There was a marked diffuse symmetrical enlargement of the thyroid gland, which also involved the isthmus. The trachea was not displaced. A fine tremor of the fingers was noted. Urinalysis gave negative results. The Wassermann reaction was negative. The basal metabolic rate was  $-5$ . The blood count was not recorded.

A diagnosis of adenoma of the thyroid gland was made.

*Operation* (Dr. W. B. Parsons; June 11).—The thyroid gland contained several small adenomatous nodules. The pyramidal lobe and the isthmus were unusually thick. The lobes were rather friable but appeared to contain abundant colloid. A subtotal resection was done on both sides with removal of the isthmus and the pyramidal lobe.

*Pathologic Report.*—The specimen consisted of portions of both lobes of the thyroid gland which measured 6.5 by 6 by 2.5 cm. and 6.5 by 4 by 2 cm., respectively. They were similar in appearance. Each was partially covered by a thin capsule. They were firm in consistency, and the cut surface had a dull grayish-white cellular appearance. No cysts or adenomas were noted.

Microscopically, sections from various parts of each showed a marked infiltration of lymphocytes. There were many diffusely scattered, but for the most part they formed large and small follicles containing frequent hyperplastic germinal centers. The surrounding acini appeared compressed. These were lined

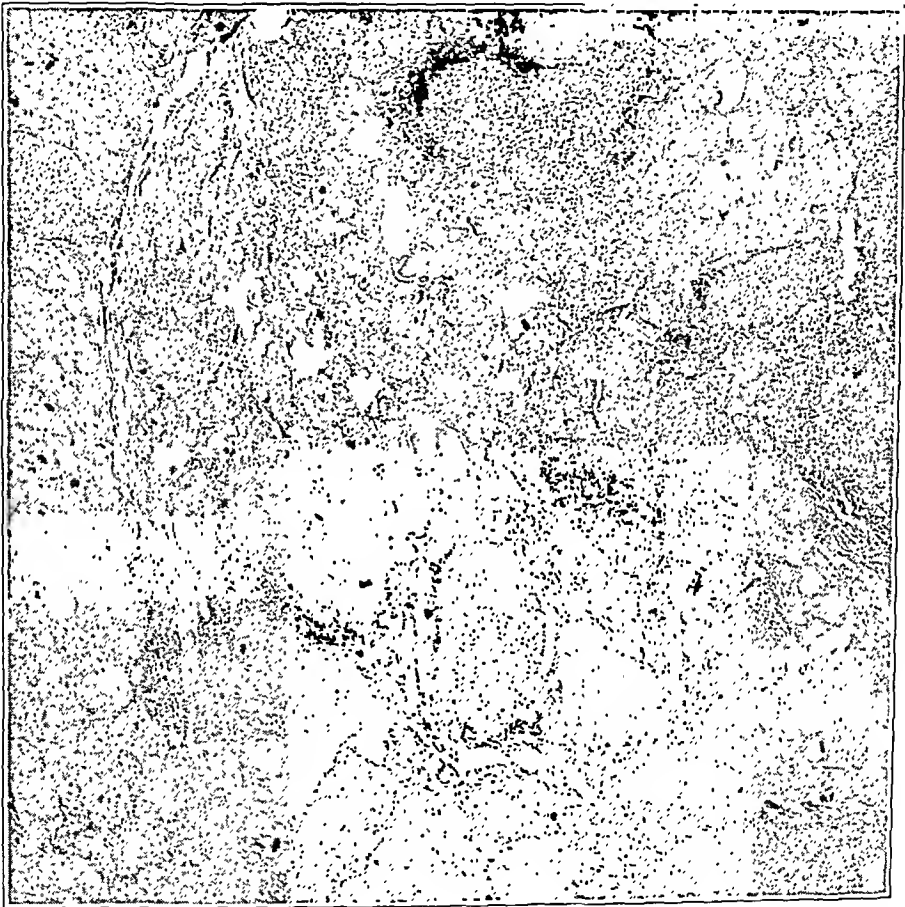


Fig. 8 (case 11).—A section of the thyroid gland in a case of thyroiditis (lymphoid type) showing the numerous lymph follicles and small acini with little colloid content. Magnification,  $\times 100$ .

by swollen, pale cuboidal cells. The nuclei were round or oval and vesicular, with a large amount of pale granular cytoplasm. Very few contained colloid (fig. 8). There was a slight increase in the interlobular connective tissue stroma. The acini showed degeneration but were without evidence of hypertrophy or regeneration. No giant cells were noted. The vessels were apparently free from pathologic change.

*Postoperative Course.*—The patient was discharged on the sixth day. The basal metabolic rate was  $-4$ . Her general condition was improved in one month. She weighed 170 pounds (77.1 Kg.). She was free from symptoms two months

after operation. There was no evidence of hypothyroidism or hyperthyroidism one year after operation. A slight increase in the remnants of the gland was noted at this time. The gland was still palpable twenty months after operation, but there were no symptoms of recurrence.

CASE 12.—*History*.—An American housewife, aged 31, was admitted to the hospital on March 15, 1934, with complaints of a goiter of fifteen years' duration and nervousness of a few years' duration. Her mother had a nontoxic goiter, and a cousin had suffered from exophthalmic goiter. When the patient was 16 years of age a physician told her that she had a goiter. This did not give rise to symptoms, and did not enlarge until during the first pregnancy, three years later. Following this the swelling receded and continued to do so after a second pregnancy, although it did not decrease to the original size. The goiter slowly enlarged again after the third pregnancy, six years before admission. For a few years before admission the patient had been conscious of the growth when she was excited or nervous. These symptoms had become more marked recently. There was no pain, tremor, loss of weight, exophthalmos, dyspnea, dysphagia or symptoms of hypothyroidism. The basal metabolic rate was not elevated, a recent reading being —9.

*Examination*.—The temperature was 98.6 F.; the pulse rate, 84, and the respiratory rate, 22. The blood pressure was 112 systolic and 78 diastolic. The weight was 109 pounds (49.4 Kg.). The patient was well nourished and did not appear acutely ill. The thyroid gland was moderately enlarged, movable and firm, but not hard or tender. The enlargement was bilateral but was most marked on the right side and at the isthmus. The regional lymph nodes were not enlarged. There was no tremor or exophthalmos. The urine was normal. The Wassermann reaction and the blood count were not recorded.

A diagnosis of adenoma of the thyroid gland (nontoxic) was made.

*Operation* (Dr. L. Sloan; March 16).—"Contrary to expectations, the gland was not grossly nodular but diffusely enlarged and lobulated. It had the appearance of a gland such as usually occurs in primary hyperthyroidism; that is, it was pale, firm, friable and vascular. The enlargement was chiefly of the right lobe and the isthmus, but the left lobe was larger than normal. The gland was not adherent to the surrounding structures or trachea."

The major portion of the right lobe, the isthmus and a wedge-shaped piece from the left lobe were removed.

#### RÉSUMÉ OF TYPES

*Fibrous Type (Riedel)*.—The onset of this type is insidious. The disease is characterized by the appearance of a hard tumor mass in the thyroid gland. Not infrequently a goiter may have been present for months or even years. This swelling, which has not given rise to symptoms, suddenly begins to enlarge rapidly, without apparent cause. The enlargement usually appears in one lobe and may remain localized, but more frequently it extends to involve the entire gland. The mass is of moderate size but tends early to become fixed to the surrounding structures and may even involve the mediastinum, but the skin rarely becomes adherent.

The symptoms seem out of proportion to the size of the tumor. Symptoms of pressure appear early, the most common being dyspnea,

which is most marked on exertion, and dysphagia, dysphonia and attacks of aphonia when the patient is recumbent. Nervousness and tachycardia, usually without tremor, may occur late. Pain is usually absent, but tenderness is not uncommon. The temperature is not elevated; the leukocyte count is normal. The basal metabolic rate remains within normal limits. The general health is not impaired. There are no associated signs of hypothyroidism or hyperthyroidism.

The tumor is extremely hard and likened to wood, iron, stone, cartilage and even bone. It is smooth or finely irregular. The edges are ill defined, especially as the tumor becomes fixed to the surrounding structures. The regional lymph nodes are not enlarged. Grossly, the capsule is usually thickened and fibrous. The gland is white and appears fibrous, and very little, if any, thyroid parenchyma can be recognized. Microscopically, this form is characterized by fibrosis, which varies in degree from marked accentuation of the interlobular and intralobular stroma to complete replacement of the parenchyma by hyalinized fibrous connective tissue. The fibrosis is usually most pronounced beneath the capsule and may extend to the surrounding structures. The remaining acini appear compressed and show varying degrees of degeneration with occasional evidence of epithelial hyperplasia. Numerous plasma cells are present. There is great variation in the numbers of lymphocytes. In many cases, of which the first six are examples, there are only small numbers of scattered lymphocytes. In cases 7, 8 and 9 there was a generalized lymphocytic infiltration with formation of follicles containing hyperplastic germinal centers. This is illustrated by figure 6. Large multinuclear phagocytic giant cells frequently occur in the areas of degenerating acini. These appear to be formed by fusion of epithelial cells around droplets of colloid (figs. 4 and 5).

*Lymphoid Type* (Hashimoto).—In contrast to the fibrous type, this form occurs almost exclusively in women. The disease manifests itself at the onset by the chance discovery of a goiter without symptoms of hypothyroidism or hyperthyroidism. Rapid enlargement usually occurs after several months. This is accompanied by symptoms of local pressure. Pain and tenderness are uncommon. The enlargement is due to changes within the capsule, and in contrast to the fibrous type the mass becomes adherent only to the trachea. There is no fever or leukocytosis. The basal metabolic rate is not elevated. The general health is not impaired.

The usual contour of the thyroid gland is preserved. The enlargement is hard, smooth and movable, and the boundaries are clearly defined.

Grossly, both lobes and the isthmus are uniformly enlarged and covered by a thin capsule. The tissue is hard and white and cuts with the resistance of fibrous tissue. The cut surface has a dense, homo-

geneous cellular appearance and is traversed by clearly defined fibrous trabeculae. Normal thyroid parenchyma or colloid cannot be recognized.

Microscopically, this type is characterized by massive and diffuse lymphocytic infiltration, with localized lymph follicles containing hyperplastic germinal centers. Plasma cells are also regularly seen. The acini show varying degrees of atrophy with degeneration of epithelium, diminution of colloid and replacement fibrosis. There is an increase in the fibrous stroma. There is nothing suggestive of tuberculosis, sup-puration or a malignant growth. The vessels show no unusual change.

#### COMMENT

*Comparison of the Two Types.*—It seems correct to separate the cases into two groups because of clinical and pathologic differences. Beyond this, many difficulties are encountered in the interpretation of the two forms as separate diseases or as different stages of the same disease. The obscure etiology makes the problem one impossible to solve at the present time. It is the impression, from the study of twelve cases and the review of reported cases to date, that the two are probably separate diseases, and that struma lymphomatosa is not necessarily followed by fibrosis, nor is Riedel's struma necessarily preceded by the former.

Many obstacles occur in reviewing the literature. Several authors have tabulated reported cases, but no two have recorded the same entire group. In the review of each case, the following factors have been taken into consideration: sex, age, history of previous goiter, symptoms of previous or present hypothyroidism or hyperthyroidism, duration of present symptoms, description of the tumor clinically and, in case of operation, the nature of the cervical infiltration, the gross and microscopic pathologic picture and the clinical and postoperative course. One hundred and sixteen records of cases have been collected, including those just presented. Cases in which there were inadequate clinical or pathologic reports and cases mentioned in the discussion of papers were excluded.

Twenty-six cases seem similar to those described by Hashimoto and ninety similar to those described by Riedel. In the former group there was only one male patient, while in the latter group twenty-nine or 32.2 per cent were men. If, then, the lymphoid type is the early stage of the fibrous type, the cases of the latter occurring in men, which represent 32.2 per cent, must either not pass through the first stage or pass through it so rapidly as to be unrecognized.

Both types occur largely in the same age period. The youngest patient with the lymphoid type was 26, and the oldest, 75. The average age of the women was 47.6 years. The one man was 50. The youngest patient with the fibrous type was 23, and the oldest, 78.

It is of interest that 73 per cent of the first group and 71.2 per cent of the second group of cases occurred in persons between the ages of 30 and 60 years.

The average duration of goiter in the first group was thirty-five months, and in the second, twenty-eight months. The duration of the symptoms in the cases of the lymphoid type was 15.4 months as com-

TABLE 1.—*Age Distribution of the Lymphoid and Fibrous Types*

	Age Period							Total
	20 to 30	30 to 40	40 to 50	50 to 60	60 to 70	70 to 80	?	
Lymphoid type (Hashimoto)								
Males.....	..	..	..	1	..	..	..	1
Females.....	2	5	8	5	3	2	0	25
Fibrous type (Reidel)								
Males.....	3	9	8	3	3	1	2	29
Females.....	7	15	20	11	5	0	3	61

TABLE 2.—*Comparison of Lymphoid and Fibrous Types*

	Lymphoid Type (25 Cases)	Fibrous Type (90 Cases)
Sex		
Male.....	1 (4.0%)	29 (32.2%)
Female.....	25 (96.0%)	61 (67.8%)
Age, years		
Youngest.....	26	23
Oldest.....	75	78
Average: Male.....	50	42.1
Female.....	47.6	43.6
Duration of goiter		
Shortest.....	3 days	30 days
Longest.....	14 years	26 years
Average.....	35 months	26 months
Number of cases.....	22	54
Duration of symptoms		
Shortest.....	30 days	15 days
Longest.....	6 years	2 years
Average.....	15.4 months	6.3 months
Number of cases.....	16	49
Thyroid involvement		
Bilateral.....	100%	70%
Unilateral.....	..	30%
Operative findings		
Diffuse cervical infiltration.....	0	50%
Postoperative hypothyroidism		
Percentage.....	40%	25%
Number of cases.....	22	63

pared to 6.3 months in those of the fibrous type. This can be explained by the absence of cervical infiltration in the former, and hence slower development of pressure symptoms.

The involvement of the thyroid gland was bilateral in 100 per cent of the cases of the lymphoid type and in only 70 per cent of those of the fibrous type. If, then, the former is the early stage of the latter, regression must have occurred in one lobe in 30 per cent of the cases.

In all the cases of the lymphoid type the process was limited by the capsule, with at the most only adhesions to the trachea, whereas in 80 per cent of the cases of the fibrous type there was diffuse cervical infiltration.

Postoperative hypothyroidism was more common in the cases of the lymphoid than in those of the fibrous type in the ratio of 40 to 25 per cent. This can be explained by the fact that it was surgically remarkable in the former group and hence was treated by more extensive excision than was possible in the cases of the fibrous type. This also explains cases of recurrence or persistence in the latter group, which required secondary operations not necessary in the former group.

*Etiology.*—The etiology is unknown. Tuberculosis and syphilis have been suspected as being factors but have been excluded by many. Numerous attempts to demonstrate tubercle bacilli and *Spirochaeta pallida* in the specimens have failed. Bohn reported a case followed by regression after removal of infected teeth with apical abscess from which "green producing streptococci and staphylococci" were cultured. Wegelin and Erkes have seen cases following "grip." Searles and Bartlett mentioned a case in which a strain of *Streptococcus viridans*, which was identical with an organism recovered from the patient's throat, was cultured from a biopsy specimen. Meeker reported a case in which the condition was associated with remnants of the postbranchial body in the thyroid gland, and suggested this as a possible route of infection. Tailhefer and Gerlak suggested the staphylococcus as a possible etiologic factor. Wegelin, however, mentioned the fact that cultures of the thyroid gland often show bacteria without any definite trace of inflammation being present.

Graham stated in 1931:

The group of cases generally classified as Riedel's disease may be looked upon as a local inflammatory process in the thyroid for which an etiological factor should be sought. In these cases the general body economy is affected only secondarily by reason of destruction of the thyroid, interference with deglutition and injuries to important blood vessels and nerves. Such a process has its counterpart in other organs and tissues, which may be expected to react similarly, except for the fact that the thyroid is so situated that complications can occur readily. The changes which occur in the thyroid in the presence of the Hashimoto type of lesion, however, may be considered primarily as a local manifestation of a constitutional disorder, the nature of which is not yet understood. What the initial changes in the thyroid may be is not yet known, but it seems clear that in the course of time these changes tend to become degenerative (rather than inflammatory) and sclerosing, and ultimately may be accompanied or complicated by more definitely inflammatory phenomena of a nonspecific character.

*Diagnosis.*—The preoperative diagnosis is difficult but not impossible. The history of rapid enlargement and hardness of the tumor, and in



many cases fixation to the surrounding structures, immediately suggests a malignant growth, especially when the disease is limited to one lobe. However, when the lesion is bilateral (carcinoma being usually unilateral), movable or adherent only to the trachea and is tender and unassociated with hyperthyroidism, enlargement of the lymph node and impairment of health, chronic thyroiditis should be suspected. When possible, roentgenograms should be taken of the long bones to exclude metastases. Examination of frozen sections at the time of operation is recommended.

*Treatment.*—Local applications of heat, cold, iodine, x-rays and radium have not proved curative, and their value is questionable.

Conservative resection of the tumor with division or removal of the isthmus is the recommended treatment. Even removal of small portions can be expected to be followed by regression of the mass. For this reason radical excision should not be attempted.

#### SUMMARY

Twelve cases illustrating the clinicopathologic features of a rare disease of the thyroid gland are reported.

The etiology is unknown. The disease is not associated with hypothyroidism or hyperthyroidism and is obviously not a malignant new growth, as metastases never occur. Clinically, the condition is most frequently mistaken for carcinoma. The general health is not impaired other than from local pressure.

There are two distinct types: a fibrous and a lymphoid type.

The fibrous type manifests itself by the appearance of a hard tumor mass. This rapidly enlarges and may remain localized to one lobe but more often extends to involve the entire gland. Diffuse cervical infiltration with accompanying symptoms of local pressure occurs early. This form is characterized microscopically by diffuse fibrosis with a varying degree of lymphocytic infiltration. There is marked atrophy of the acini, with the formation of large multinucleated phagocytic giant cells.

The lymphoid type manifests itself by the sudden rapid enlargement of a goiter of several months' duration. The growth is bilateral and hard and becomes adherent to the trachea only. This form is characterized microscopically by a dense infiltration of lymphocytes and the formation of lymph follicles with hyperplastic germinal centers. Varying degrees of degeneration of the acini occur, with associated fibrosis.

The two types have been generally accepted as different stages of the same disease. It is the conclusion from the study of twelve cases and the review of reported cases that these forms are probably separate and distinct entities.

The course of the disease is benign. Total removal of the growth is not necessary. Partial conservative resection is the recommended treatment. Recovery with subsequent good health is to be expected. Recurrence is rare.

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## A REVIEW OF UROLOGIC SURGERY

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### KIDNEY

*Anomalies.*—Marcucci<sup>1</sup> reviewed the malformations of the urinary apparatus that may give rise to renal disorders. After making a detailed study he concluded that all such malformations may at times produce disease within the kidney. Every malformation has its own particular relation to the determination of pathologic change in the body; this is revealed in cases of renal changes which generally are the results of urinary obstruction. Some of them produce stagnation by mechanically obstructing the normal progress of the renal secretion; others apparently disturb the harmony of muscular action on which urinary excretion depends, since the calices, pelvis and ureter constitute a single dynamic, harmonic complex. Others express a constitutional deficiency, either myogenic or neurogenic, in the pyelo-ureteral excretory system; that is, in the various parts to which the transportation and regulation of the urine is delegated.

As is always the case with any organic fluid which becomes stagnant, the retained urine easily becomes infected and constitutes the basis for formation of calculi, which have a twofold effect: They increase retention by mechanically obstructing the urinary outlet, and they cause inhibition or spasm of the musculature of the ureter. Suppuration continues to impose a fatal burden on the already diminished functional and anatomic integrity of the renal apparatus. In proportion to the quantity of toxic elements that it brings into contact with the pyelo-

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1. Marcucci, Guiseppe: Rapporti fra anomalie ed affezioni renali, Arch. ital. di urol. 11:427 (Aug.) 1934.

ureteral musculature it induces spasms, hypertonia and retention, or it produces atony through degenerative changes that it brings about in the muscular tunics and leads to dilatation.

Stasis favors infection, and infection maintains stasis; the resulting retention, which increases progressively by virtue of these two factors reciprocally augmenting one another, is the expression of the continuous decadence of the excretory duct; this decadence is first dynamic, then anatomic, and is revealed in the kidney by nephritis, pyelonephritis, hydronephrosis, hydropyonephrosis, pyonephrosis and calculosis.

*Tumors.*—Priestley and Broders<sup>2</sup> reported that Wilms' tumor, also called embryoma or embryonal adenocarcinoma of the kidney, was diagnosed in 65 cases at the Mayo Clinic. Thirty-seven of the patients gave evidence of advanced disease at the original examination and received irradiation or symptomatic treatment alone. The remaining 28 were subjected to operation, 20 undergoing nephrectomy. Forty-four of the 65 patients were followed. Clinical evidence of this disease usually becomes manifest only after advanced pathologic changes have taken place in the kidney. An abdominal mass in the region of the kidney involved was the most common initial complaint (in 40.5 per cent of the patients it occurred as the initial symptom), and it was present in all but 1 patient at the time of examination at the clinic.

According to Priestley and Broders the differential diagnosis of Wilms' tumor seldom affords much difficulty, although occasionally hydronephrosis, polycystic kidney, solitary cyst of the kidney and various retroperitoneal tumors may be confused with this lesion. To mistake the condition for hydronephrosis is the most common error in diagnosis, as in both this condition and in Wilms' tumor a cystic-feeling mass, associated with fever, may be present. Gradual growth of the mass and hematuria indicate the presence of a neoplasm. The two most valuable aids in establishing the diagnosis of Wilms' tumor are intravenous urography and the fact that there is remarkable diminution in the size of the mass after roentgen therapy.

Considerable divergence of opinion exists regarding the proper method of treatment of this type of tumor. Some authors favor irradiation alone and regard nephrectomy only as a procedure that promotes early metastasis; others hold an opposite opinion. Priestley and Broders expressed the belief that the most satisfactory treatment includes preoperative roentgen therapy, followed at an appropriate time by surgical removal of the lesion and subsequently by irradiation. The amount of roentgen treatment used preoperatively is regulated by the dose tol-

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2. Priestley, J. T., and Broders, A. C.: Wilms' Tumor: The Most Common Malignant Growth Affecting Children, *Proc. Staff Meet., Mayo Clin.* **10**:81 (Feb. 6) 1935.

erated by the patient and by the therapeutic response, as evidenced by decrease in the size of the tumor. At least one course of treatment should be given, and sometimes a second series is indicated. The optimal time for operation exists when the maximal therapeutic response has been obtained and is prior to a secondary increase in the size of the tumor. This usually requires a period of from three to six weeks. Excessive irradiation may be detrimental to the normal development of children.

The results of treatment of Wilms' tumors in the past have been discouraging. Of the 44 patients in this series who were followed, 40 are dead, and not a single patient is living who was treated by irradiation only. Of the 4 patients who are living at present, 1 has survived thirteen and a half years; 1, three and a half years, and 2, ten months each. Since the introduction of combined irradiation and surgical treatment in cases of Wilms' tumor more favorable results have been obtained.

Taylor<sup>3</sup> stated that the etiology of papillary carcinoma of the pelvis is not known. Chronic irritation in the pelvis probably accounts for initiation of these growths. Few papillary growths have followed chronic infections and calculi have been associated with only about 5 per cent of such growths. In the nonpapillary group of tumors infections, leukoplakia and stones have played a much more prominent rôle as possible exciting factors. The chief characteristic of papillary tumors of the pelvis is surface metastasis. This is evident clinically. According to Taylor, Stricker reviewed 175 cases of papillomatous tumor of the renal pelvis and found that the same type of tumor was found concurrently in the ureter and in the bladder in 47 per cent of the patients. In 35 per cent of cases in which nephrectomy was performed for papillary tumor of the pelvis recurrence in the ureter or bladder appeared later. Taylor referred to Kimball and Ferris, who in a similar study found 74 cases in the literature, in 50 of which tumors occurred in the ureter or bladder after nephrectomy; they also found 24 cases in which the ureter and bladder were affected at the time of examination or operation. Hematuria is the most frequent and usually the first symptom. It is the only symptom in about one fourth of the cases. It is present some time in the course of the disease in 70 per cent of cases of papillary tumor of the pelvis. Because of the marked vascularity of the tumors they usually bleed early, abundantly, intermittently and without any exciting cause. Pain is a variable symptom and depends on distention of the pelvis, which in turn is attributable to obstruction, either by clot or tumor, at the ureteropelvic juncture. Lumbar aching or discomfort may be annoying; it is usually a distention type of distress

3. Taylor, W. N.: Papillary Epithelioma of the Renal Pelvis, *J. Urol.* **33**: 531 (June) 1935.



and is attributable to the associated hydronephrosis. Ureteral colic may result from the passage of either blood clots or fragments of tissue from the tumor. The passage of particles of tissue is another clinical finding which may be indicative of the lesion. These particles may be found in the urine, or the patient may recall having passed such particles. Vesical symptoms depend on irritation complicating the lesion. Frequency, dysuria and inability to void are usually attributable to stone, infection or blood clots in the bladder. Constitutional symptoms, such as loss of weight, anemia and asthenia are late manifestations and are usually associated only with metastasis. The lesion is practically never diagnosed from the history, the symptoms or the physical examination. Cystoscopy is of definite value only when there are tumors in the bladder, and these are presumptive evidences only when they are situated about, or are protruding from, the ureteral orifice of the involved kidney. The tendency to implantation on the mucosa of the ureter and bladder demands surgical removal of the kidney, ureter and a section of the vesical wall for complete eradication of the disease.

Sprenger and Bohrod<sup>4</sup> reported 2 cases in which the presence of bilateral renal carcinoma was proved at necropsy, together with certain clinical findings, and reviewed the literature concerning bilateral renal new growths of this type. The literature shows that this condition occurs rarely. Sprenger and Bohrod stated that Chute, in 1926, reported 43 cases of renal carcinoma including 1 in which involvement was bilateral and that Sanford reported a case in which there was carcinoma of both kidneys and in his studies found 4 similar cases.

Necropsy in the first case reported by Sprenger and Bohrod revealed that the right kidney was about one and a half times normal size. Near the hilus there was a fairly well encapsulated tumor 5.5 cm. in diameter. It was soft, and its cut surface was mottled with red areas of hemorrhage on a bright yellow background. Neither the pelvis nor the renal vein was invaded by the tumor, although the pelvis was compressed and markedly distorted. The region of the left kidney and the entire retroperitoneal space between the vertebral column and the lateral abdominal wall were occupied by a large tumor. On section, about three fourths of the mass was seen to be composed of an enormously enlarged kidney, the hilus and most of the upper pole of which were occupied by soft yellow tumor tissue. The pelvis was dilated and filled with pus. The ureter was thickened but free from tumor tissue. In the upper lateral portion of the kidney the tumor had broken through the capsule, and all the perirenal tissues were invaded by the tumor. The renal vein was free from tumor tissue. There was no metastasis anywhere. The

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4. Sprenger, Arthur, and Bohrod, M. G.: Bilateral Renal Carcinomas, *J. Urol.* **33**:427 (May) 1935.

histologic appearance of the two tumors was alike, even in its variability. In most places the tumors were composed of large, clear cells filled with lipid. In other places the cells were granular, stained more deeply and gave evidence of much more anaplasia. In these portions, especially, there were greatly dilated blood sinuses. Distinct papillary structures were present in both tumors, often occurring in the same slide with hypernephroid structures. Areas of necrosis and hemorrhage were numerous.

In the second case necropsy revealed that both kidneys were the sites of tumors. The hilus of the left kidney pointed directly anteriorly. The lower pole was occupied by an irregular tumor which, on section, was seen to be made up of two incompletely separated portions. The internal portion was composed of white tissue with a necrotic, gelatinous center. The external part was much firmer and of lighter color. Small, cystic portions and regions of hemorrhage were present. The right kidney was larger than the left. Most of the middle segment and almost all of the lower pole were occupied by an irregular tumor. On section this tumor was seen to be lobulated, bright yellow, with cystic portions and small regions of hemorrhage. The renal vein was short and filled by the same kind of tumor tissue. Metastatic growths were found in small number but were present in many organs. By direct extension from the left kidney, the tail of the pancreas was involved. There were several small, metastatic nodules in the body of the pancreas and a few large metastatic growths in the liver. Both adrenal glands contained metastatic growths. In the lung there was a single tumor nodule. The histologic appearance of the metastatic nodules was remarkably constant. The cells were large and clear, with small pyknotic nuclei. They were separated into groups by thin trabeculae of connective tissue. The cytoplasm was filled with lipoids. Areas of necrosis were common. The tumors in the two kidneys evidenced much variability. Although they were mainly composed of large, clear cells filled with lipid, there were also many irregularly arranged and some giant-sized tumor cells. Large, blood-filled sinuses gave to some sections an appearance of pseudo-hemangiomatosis. The variability in the tumor of the left kidney was greater than that in the right.

According to Sprenger and Bohrod, the presence of bilateral renal carcinoma leads to some interesting considerations with regard to the pathogenesis of renal tumors. Multiple tumors are no longer considered to be as rare as they seemed to be in the past. Collections of large statistics appear to indicate that they are more frequent than they would be if they could be accounted for only by coincidence. This may indicate that some persons have a specific tendency to neoplasia. In the first case reported herein, in addition to the two tumors of the kidneys there were multiple hemangiomas in the skin, a hemangioma in the liver

and a benign adenoma in one kidney. Bilateral renal tumors, except for embryonal tumors and multiple tumors occurring in sclerotic kidneys, are exceedingly rare, and their rarity is especially noteworthy when it is realized that renal tumors are common.

In the genesis of every malignant tumor there is interplay of two distinct factors, an intrinsic one, the hereditary substratum, and an extrinsic one, the stimulus which is directly responsible for the malignant transformation of a hitherto quiescent cell or group of cells. The kidneys are protected against localized external influences. Stimuli which may come through the urine influence all parts of the kidney equally and simultaneously. Sprenger and Bohrod assumed that in some way the two kidneys are different at birth. The only difference lies in the presence of localized accumulations of embryonic cells arranged to form the so-called adenomas such as are found relatively frequently by accident at necropsy, but which may, as in 1 of their cases, be microscopic. The rare occurrence of bilateral renal carcinomas is, therefore, support for the contention that these tumors arise from embryonic cell rests or from benign adenoma-like nodules. The occasional occurrence of bilateral or multiple tumors is probably associated with the presence of multiple rests.

Waters<sup>5</sup> stated that tumors of the hypernephroma type and embryonal carcinomas are radiosensitive. Papillary carcinomas of the renal pelvis and the malignant, papillary cystadenomas are radioresistant. Irradiation has caused marked reduction in the size of radiosensitive renal tumors and has rendered operable tumors which had been inoperable because of their large size. Irradiation has produced in sensitive tumors extensive morphologic changes characterized by alterations in cellular structure, extensive fibrosis hyalinization and necrosis. The cells become shrunken. The cytoplasm may contract around the nucleus, and in certain cases the tumor has been completely destroyed and replaced by fibrous tissue. Palpation of the tumor should always be avoided as much as possible to prevent expressing tumor cells into the blood stream. Reduction begins almost immediately after institution of irradiation and continues for several weeks after cessation of treatment. Operative removal is imperative and should be performed within a few weeks after either the first or second series, depending on the degree of shrinkage of the tumor as revealed by palpation and retrograde pyelographic studies. Regrowth of the tumor may, and has, occurred after too long delay of operation. Preoperative irradiation has not made operation more difficult. In order to lessen the mortality in cases of tumor of the kidney an early diagnosis must be made. Great significance must be

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5. Waters, C. A.: Preoperative Irradiation of Cortical Renal Tumors, *Am. J. Roentgenol.* **33**:149 (Feb.) 1935.

attached to hematuria and pain. The retrograde pyelogram helps to distinguish between pelvic and cortical tumors in from 80 to 100 per cent of the cases, and, in Waters' experience, 93.4 per cent of all cortical renal tumors have been radiosensitive.

Wharton<sup>6</sup> stated that a review of the literature shows that results of the surgical treatment of renal tumors are unsatisfactory. From 5 to 10 per cent of such tumors are considered inoperable because of size or metastasis, and in from 12 to 26 per cent of the cases nothing is done after exposure for the same reasons. The mortality from surgical shock after nephrectomy is between 15 and 30 per cent, and cure is permanent in less than 10 per cent of the remaining cases. Ninety per cent of children with renal tumors die within the first year after operation.

The unsatisfactory situation is caused largely by the fact that these tumors at the time of operation are large and friable and have thin capsules. The manipulation necessary in removing these enormous masses results in showers of distant metastatic growths and rupture of the capsule, with local recurrence. There are also technical difficulties because of the size of the tumor, with accompanying shock, hemorrhage and injury to important contiguous structures.

Wharton recommended preoperative irradiation to reduce the size of the tumor and the transperitoneal approach to minimize handling and to permit ligation of the renal vessels as the first step in removal of the tumor. Preoperative irradiation causes a rapid and striking reduction in size of the growths, especially of embryomas of children, and permits satisfactory surgical removal. During the three weeks' course of radiotherapy and there must be careful medical supervision, and a special diet, rest, tonics and transfusions are prescribed when necessary.

Wharton reported his experience in several cases which he divided as follows: Group 1 was composed of 2 cases of massive tumor in which preoperative irradiation was not given. Group 2 included 3 cases in which massive tumors were removed after preoperative irradiation. Group 3 was made up of cases in which small tumors were removed without irradiation.

Wharton<sup>7</sup> described and illustrated the steps of a simple method of performing transperitoneal nephrectomy, which makes it possible to remove malignant tumors of the kidney with a fair degree of safety and a minimal likelihood of rupturing the mass. This procedure tends to dissipate the current opinion that transperitoneal nephrectomy is a dangerous and complicated operation. It is Wharton's opinion, and also

6. Wharton, L. R.: Preoperative Irradiation of Massive Tumors of the Kidney, *Arch. Surg.* 30:35 (Jan.) 1935.

7. Wharton, L. R.: Transperitoneal Nephrectomy for Malignant Tumors of the Kidney, *Surg., Gynec. & Obst.* 60:689 (March) 1935.

that of many other surgeons, that transperitoneal nephrectomy is safer than lumbar nephrectomy for removal of tumors of the kidney. Pre-operative irradiation makes it possible to remove surgically many of these large tumors by reducing their size appreciably.

Bothe<sup>8</sup> stated that the embryonal sarcomatous cells of mixed tumors of the kidney are radiosensitive, whereas the epithelial cells in mixed tumors of this organ are radioresistant. When a mixed tumor of the kidney is irradiated before surgical removal the size of the neoplasm is usually reduced. This decrease in size of the growth following roentgen treatment appears to be dependent on the amount of embryonal sarcomatous tissue. Irradiation of the tumor does not completely destroy all the malignant cells. Mixed growths of the kidney should always receive sufficient preoperative irradiation and be removed afterward. Surgical delay results in subsequent growth and metastasis.

Dos Santos<sup>9</sup> stated that there are cases in which arteriography may clear up diagnoses that are indecisive in cases in which pyelography is insufficient. These are, especially, cases in which the diagnosis may be between renal or pararenal tumor on the one hand, and hydronephrosis or hematuric nephritis on the other. There are cases of hydronephrosis in which catheterization of the ureter is impossible and cases of hematuric nephritis in which pyelography gives somewhat doubtful results, making it impossible to affirm whether or not a neoplasm is present. It is, therefore, well worth while to note what arteriography can reveal with reference to tumors of the kidney.

There are three essential classes to be recognized in arteriographic study of tumors: hypernephromas, other cancers and vascular tumors. Hypernephromas, in the arteriogram, give images of ischemia by the side of vascular networks of the unaffected renal tissue. The larger the tumor, the more reduced will be the preserved parenchyma. Other types of malignant neoplasm, not hypernephroma, are more strongly vascularized, giving the image of an irregular circulation composed of newly formed vessels, such as dos Santos<sup>10</sup> has described elsewhere. It is not the hyperemia of inflammatory states, attributable to vasodilatation of a preexisting vascular network, but a new, improvised network, in which the course and also the lumens of the vessels are irregular, interrupted here and there by images corresponding to lakes of blood.

The aspect presented by vascular tumors (angiomas) is illustrated by a case in which the arteriogram revealed a bilaterality of the lesions,

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8. Bothe, A. E.: Tissue Changes in Mixed Tumors of the Kidney After Roentgen Therapy, *J. Urol.* **33**:434 (May) 1935.

9. dos Santos, Reynaldo: L'aortographie dans les tumeurs rénales et par-rénales, *Arch. d. mal. d. reins* **8**:313 (May) 1934.

10. dos Santos, Reynaldo: Tumeurs malignes des membres, Paris, Masson & Cie, 1932.

unsuspected before. The most striking feature in the stereo-arteriogram was the abnormal development of the circulation of the left kidney, the dilatations and lakes of blood which reached two large branches of the renal artery, only the lower pole of the kidney appearing normal. In the right kidney, unexpectedly, a similar neoplastic aspect involved one branch of the renal artery; only at the poles was this kidney normal. The belief that this was a case of vascular tumors involving both kidneys, in which only the tumor of the left side had been diagnosed previously, was confirmed by exploratory laparotomy.

The impressive difference between these images and those of tuberculosis, hydronephrosis and, most of all, hematuric nephritis, makes clear the interest that this method has in relation to the symptomatology of renal neoplasms. It is true that the arteriogram in cases of hydronephrosis often resembles that in cases of hypernephroma, the ischemia comparing with the occasional enormous development of the tumor, but the ischemia of hydronephrosis extends throughout the kidney just as does the sclerosis and atrophy of the distended parenchyma, while in cases of hypernephroma one can always recognize a part of the kidney that is entirely spared, the normal vascular network contrasting with the ischemia of the neoplastic zone.

But it is in differential diagnosis between hematuric nephritis and renal tumors that this new method plays its most important rôle. Dos Santos described several illustrative cases, in which the presence of a tumor was ruled out by the absence of the characteristic neoplastic ischemia and the absence of any abnormality in circulation; hence the diagnosis of hematuric nephritis was established.

Not only in the diagnosis of renal tumors but also in the diagnosis of pararenal neoplasms does arteriography give decisive information, and not only with reference to the existence of a tumor, but also as to its localization, differentiating, on the right side between the kidney and liver or gallbladder, and on the left, between the kidney and spleen. The images of hydatid cysts of the liver and of splenomegaly, that dos Santos has described on a previous occasion, suffice to show that in doubtful cases a diagnosis may be reached easily. Any pararenal tumor, whether of the liver, spleen, pancreas or bed of the kidney, may, by compressing the renal pedicle, cause an ischemia which lowers the functional capacity of the parenchyma without the kidney's being the seat of the trouble. Functional tests must therefore be interpreted in the light of these possibilities, which arteriography has revealed. This compression of abdominal or pelvic vessels by tumors is a fact of a general order which arteriography has made it possible to point out from the beginning of these researches. Finally, in cases of retroperitoneal pararenal tumors, in which it is difficult to establish a differentiation from

renal tumors, arteriography is the surest means of identifying the situation, and sometimes the nature, of the neoplasm. Thus, in an illustrative case, pyelography disclosed marked deformation and distention of the calices, suggesting that the tumor was indeed renal, and in addition renal function as evidenced by excretion of indigocarmine was diminished on the side of the tumor, but arteriography disclosed that both left and right renal arteries were normal, and the contour of the kidney on the side of the tumor was also absolutely normal and incompatible with a tumor of the kidney. The tumor, probably a hydatid cyst, was, therefore, extrarenal, pushing the kidney downward and inward. Other illustrative cases also serve to reenforce the view that renal arteriography is a method that should claim the attention of every urologist.

Beer<sup>11</sup> reported on five-year cures in cases of neoplasm of the bladder and kidney in which treatment or operation was performed before 1930. Considerable confusion has been introduced into the study of end-results of treatment in cases of tumor of the bladder as a result of attempts at grading the malignancy of the tumors. Eleven patients who had noninfiltrating carcinomas were cured by transurethral fulguration or electrocoagulation with high frequency current; this number of patients represented 55 per cent of the total so treated and not lost to observation. Four patients who had noninfiltrating or moderately infiltrating papillary carcinoma were cured by transurethrally introduced radium, usually together with electrocoagulation; they represented 11 per cent of the total so treated and not lost to observation. Ten patients who had infiltrating, papillary carcinomas involving the wall of the bladder more or less diffusely were successfully treated by operative excision; they represented 55.5 per cent of the total in this classification and surviving the operation. Fourteen patients who had infiltrating, solid, ulcerating, more or less papillary carcinomas diffusely involving the wall of the bladder were satisfactorily treated by extensive resection, frequently with reimplantation of the ureter, 40 per cent of the total so treated surviving the operation. Two patients who had the same type of carcinoma were cured by suprapubic cystostomy and implantation of radon seeds, 10 per cent of the total so treated surviving the operation. Four patients who had extensive, solid, ulcerating, more or less papillary carcinomas diffusely involving the wall of the bladder were cured by total cystectomy, 57 per cent of the total so treated surviving the operation. With cauterization—diathermy or electric cautery, or Paquelin cautery—and high voltage roentgen therapy, there were no five-year cures among patients with carcinoma infiltrating more or less diffusely the wall of the bladder.

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11. Beer, Edwin: Some Remarks on Five Year Cures in Malignant Tumors. Surg., Gynec. & Obst. 60a:479 (Feb.) 1935.

There was a total of 45 cures among patients with definite carcinoma treated before 1930. Owing to the advanced age of many of these patients when they presented themselves for treatment, their life expectancy scarcely warrants a five-year survival, and many more patients in each category were apparently cured, as there was no evidence of recurrence for periods of less than five years but sufficiently long to assume that cure had taken place.

According to Beer, the results in cases of malignant degeneration of the kidney must be divided into two categories: (1) hypernephroma or clear cell carcinoma, adenocarcinoma, papillary and squamous cell carcinoma of adults, and (2) embryoma, Wilms' tumor and sarcoma usually observed in children. There were no five-year cures in cases of Wilms' tumor or embryoma of children before 1930. One child with a hypernephroma was cured for more than five years, making the percentage for this group of 7 cases in which nephrectomy was performed only 16.66. Among adults, before 1930 there were 7 five-year cures among patients who had tumors of the kidney of the hypernephroma and adenocarcinoma and papillary carcinoma types, 1 five-year cure in a patient with a large embryoma or tumor of the Wilms' type and 1 five-year cure in a patient with a carcinoma of the ureter; 9 patients in all out of 34 survived the operation and were followed, making more than 26 per cent.

*Stone.*—Stevens<sup>12</sup> stated that the presence of calculi simultaneously in the upper parts of the two urinary tracts is not uncommon. There is no dependable method of dissolving calculi, but stones may pass spontaneously through the urinary channels or be removed by operation. Large, noninfected, nonobstructing, symptomless, stag-horn calculi are usually left alone. There is also questionable advantage in trying to remove a large mass of nonobstructing, symptomless, small stones occupying an entire kidney; it is nearly impossible to find all of them, even with roentgen control at the operating table, and the kidney is usually mutilated in the attempt. It is not necessary to operate early for small, symptomless stones in a kidney, even in the presence of low grade infection, whereas it is not advisable to wait any considerable time for spontaneous passage of calculi of the ureter associated with infection of the urine. Stones of moderate size that are trapped in a calix need not be disturbed unless there is also persistent infection or unless symptoms are present.

The reasons for operating in cases of urinary lithiasis are that calculi of the upper part of the urinary tract are a serious menace when they obstruct urinary flow; they are potent in prolonging infection, and they

12. Stevens, A. R.: Bilateral Urinary Calculi with Special Reference to Therapeutic Problems, J. A. M. A. **104**:1289 (April 13) 1935.



may cause pressure atrophy of the parenchyma by growth of the stone. Ureterotomy is one of the less hazardous major operations. Pyelotomy entails added risk, and nephrotomy, particularly if extensive, is even more dangerous.

Stevens concluded, from a study of the literature and a review of 35 cases of bilateral urinary calculus in which operation was performed, that operation may not be advisable, or may be performed primarily on both sides or on one, depending on conditions. Treatment of lesions of this type must not be by stated rules and formulas, such as those which advise to operate first on the side of the better kidney, or of the worse kidney, or of the most recent pain; it must depend on definite knowledge of the immediate and remote objectives sought, of the means of attainment of these objectives, and of the risks involved. Improvement of renal function, primarily and eventually, control of infection and alleviation of symptoms should be sought. The first motive is usually outstanding, but relief from acute infection may demand initial attention, even nephrectomy.

Swick<sup>13</sup> stated that the usual history in cases of bilateral calculus of the urinary tract consists of recurrence, infection and renal insufficiency. For these reasons and because of difficulties encountered in coping with this problem, every attempt at conservative measures directed toward maintenance of renal reserve, both in the diagnosis and in the preoperative and postoperative care, must be made. Because practically all bilateral renal calculi are mainly composed of calcium phosphate and oxalate, and are therefore radiopaque, retrograde pyelography not only becomes unnecessary in many cases of such calculi but may be dangerous to the renal reserve. In cases of bilateral renal calculosis, in which in many instances the renal reserve is already compromised, retrograde pyelography may be the turning point in bringing about either uremia or urosepsis or both. Since the stag-horn, soft and fragmented type of stone is often encountered in cases of bilateral calculus of the kidney, the advantage of roentgen control at the operating table, as an adjuvant in the handling of such cases, is apparent.

Treatment of the patient should not end with the operation but should be followed along lines such as administration of the vitamin A diet; consideration of the possible relationship of hyperparathyroidism to renal calculi; recognition of the importance of constant forced intake of fluids; investigation of the reaction of the urine and the chemical composition of the stone removed, which should be determined in order to prescribe diets and medication more intelligently and, finally, in the presence of infection after removal of stones, use of the ketogenic diet.

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13. Swick, Moses, in discussion on Stevens.<sup>12</sup>

Cahill<sup>14</sup> stated that calculous anuria, the condition that accompanies suppression of urine caused by stone in the kidney or ureter, occurs under the following circumstances: Two secreting kidneys may have both ureters or pelves blocked, either synchronously or one after the other; a single secreting kidney may be blocked, the other being imperfectly developed, having been destroyed by disease or having been previously removed; both kidneys or a double kidney may have a fused, single ureter, which may be blocked by a calculus; of two kidneys, apparently normal, one may be blocked and the other may fail to secrete because of reflex reactions, the so-called renorenal reflex block, that are set up. Cahill added an analysis of 22 cases of this disease, from the Squier Urological Clinic, to the collection of 355 cases obtained from the literature by Rubritius. Among the 377 cases of calculous anuria, bilateral calculi occurred in 92 cases (24.4 per cent), unilateral calculi with disease of the opposite kidney in 45 cases (11.9 per cent), unilateral calculi with the condition of the opposite kidney being unknown in 53 cases (14 per cent), unilateral calculi with the opposite kidney being absent, removed or aplastic in 128 cases (33.9 per cent) and unilateral calculi with reflex inhibition of the opposite kidney in 59 cases (15.6 per cent).

Diagnostically, the pain and anuria have been the most significant symptoms. Cystoscopy, in conjunction with pyelograms made after retrograde injection pyelograms, was the most important diagnostic procedure. Intravenous urograms were not satisfactory. The kidneys that failed to excrete the dye gave no shadows on the roentgenogram. In 9 of the 22 cases (40 per cent) there was no shadow of calculus on the roentgenogram of sufficient density to allow a diagnosis to be made. Relief of the obstruction is the first step in the treatment of calculous anuria. The various procedures used for this were cystoscopy and extraction of the calculus, insertion of a ureteral retention catheter past the obstruction with subsequent extraction of the calculus, ureterotomy with removal of the calculus, pyelotomy with removal of the calculus, and nephrostomy, single or double, with or without removal of the calculus.

In cases of bilateral obstruction, the operation on both sides was performed at one sitting. The kidney obstructed last was operated on first in each instance. After relief from obstruction there were marked changes in the patient's symptoms. Before operation the patient usually had a dry skin and lacked thirst; after operation there was profuse sweating and return of thirst. In the cases in which no infection was present there was rapid secretion of urine and elimination of the retained

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14. Cahill, G. F.: *The Medical and Surgical Treatment of Calculous Anuria*. J. A. M. A. **104**:1306 (April 13) 1935.

urea from the blood. In the cases in which infection was present secretion often did not start until twenty-four or forty-eight hours after nephrostomy.

In the recovery of patients with calculous anuria the underlying principles appear to be the ability of the kidney to overcome the infection and to restore or improve its physiologic function. Sufficient proof has been given, experimentally and clinically, that a short block does not appreciably injure a kidney. In the early treatment in these cases the profuse forcing of fluids by subcutaneous and by intravenous administration of solutions of dextrose in various concentrations has been of value clinically to bring about the return of renal secretion. If secondary anemia was present in the patients with infection the renal output rose rapidly as the content of blood was restored toward normal. This was accomplished by means of transfusions of whole blood. In some cases, restoration of renal secretion followed only transfusion. In Cahill's experience renal lavage has not been followed by satisfactory results. It has prolonged the fever and symptoms in cases in which infection has been present and has not proved of value in the prevention of recurrence.

Trattner<sup>15</sup> stated that of 157 patients with lithiasis of the urinary tract admitted to the Cleveland City Hospital, 14 were found to be partially or completely anuric. Eight of the 14 were moribund when first observed and died shortly afterward. It is apparent that partial or complete suppression of urine in the presence of lithiasis is an emergency problem.

Decapsulation of the kidney would be of benefit if the kidney should be under tension, for the renal capsule is reflected from the vessels at the hilus and mechanically retards the venous flow from the kidney when stretched. Decapsulation may also be of value in permitting cortical abscesses of the kidney to drain. When the kidney is buried in dense adhesions it is much safer to mobilize it intracapsularly, particularly on its anterior surface, than to attempt a dissection of the adhesions with the risk of opening the peritoneal cavity. Nephrectomy is contraindicated in cases of calculous anuria because renal tissue, regardless of the amount, must be conserved even though a considerable portion of it is diseased. Ureterotomy at a low level for removal of the calculus is definitely contraindicated, but ureterotomy at a high level for drainage and removal of the calculus, if in that vicinity, is permissible. Nephrostomy is frequently an important procedure. Pyelotomy is of value, permitting extraction of stones from the renal pelvis and drainage without destruction of renal tissue. Venesection and transfusion should be performed as quickly as possible if the hemoglobin is not reduced too

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15. Trattner, H. R., in discussion on Cahill.<sup>14</sup>

much; or, if it is reduced, a transfusion alone, without venesection, should be given.

Watson,<sup>16</sup> in discussing calculous anuria, stated that Cahill's experience in handling 22 cases of this condition shows several important basic principles. Despite the fact that in 9 (40 per cent) of the 22 cases there was no diagnostic shadow on the plain roentgenogram, Watson expressed the belief that the making of a plain roentgenogram should be the first step in cases of this type. As a second step, every effort should be made to pass a ureteral catheter at least part way up the ureter. On several occasions it has been possible to pass a small catheter 1 or 2 cm. beyond the obstructing calculus in the lower part of the ureter of a single kidney and establish drainage. With drainage even imperfectly established the situation can often be changed from one demanding immediate, emergency operative intervention to one of elective operation at a more opportune time. Even in cases of bilateral calculus of the pelvis the passage of a catheter to the pelvis and beyond the stone may establish adequate drainage and may help to prepare the patient for subsequent operation. When readily possible, drainage by pyelotomy is the procedure of choice in cases of calculous anuria not associated with infection or in those in which only mild infection is present. Large renal calculi may sometimes best be handled by nephrotomy. In most instances thorough lavage of the interior of the kidney at operation, with from 1 to 2 quarts (1 to 2 liters) of saline solution, aids in controlling bleeding and may wash out a few small calcareous particles that might later serve as nuclei for further formation of stone. In cases of bilateral involvement operation on both sides (other than drainage) at a single sitting is not considered advisable by Watson.

In a review of 162 cases of stone in the upper part of the urinary tract, Winsbury-White<sup>17</sup> discussed the etiology, clinical features and diagnosis, and particularly the treatment. Despite experimentation with animals to show that dietetic errors influence formation of renal calculi, it is doubtful whether the mixed regimen followed by a modern community has any important bearing on the formation of stone.

The two factors of prime importance are dilatation of the upper part of the tract and a chronic focus of infection in the pelvic organs. The focus may be in the prostate gland and seminal vesicles in male, and in the uterine cervix and adnexa in female, patients.

An important clinical feature of renal lithiasis is absence of symptoms in many cases. The onset of pain and hematuria depends fre-

16. Watson, E. M., in discussion on Cahill.<sup>14</sup>

17. Winsbury-White, H. P.: A Review of One Hundred and Sixty-Two Consecutive Personal Cases of Stone in the Upper Urinary Tract, *Brit. J. Urol.* 6:142 (June) 1934.

quently on a definite increase in, or activity of, existing infection, and one must avoid the pitfall of regarding the absence of physical signs as excluding the presence of stone.

Excretory urography is valuable in establishing the diagnosis, the exact situation of the stone, the renal functional activity and the amount of dilatation.

Treatment is discussed under the following subdivisions: (1) small stones capable of passing; (2) presence in one kidney of a stone too large to pass, (*a*) without gross renal impairment or infection, (*b*) with gross renal impairment or infection; (3) presence in one kidney of a stone formed secondarily to hydronephrosis, (*a*) with unilateral dilatation, (*b*) with bilateral dilatation; (4) presence of stones in both kidneys.

There is scope for a considerable variety of treatment, depending on degree of infection, renal function, obstruction and pyelectasis. Recurrences are avoided by complete removal of all fragments, aided by roentgenograms of the exposed kidney. Excision and resection of thinned out and devascularized renal tissue and calices prevent persistence of "pooling" and of pelvic residual urine and is a sound safeguard against recurrences.

Plastic repair of the ureteropelvic junction should be performed whenever obstruction occurs at that point. Nephrectomy rather than a conservative operation is advisable in many cases of unilateral stone, to insure against pyuria, further formation of stone and continued ill health.

In the 43 cases of unilateral involvement in which nephrectomy was performed subsequent formation of stone on the opposite side did not take place in any case. Occasionally nephrectomy is indicated in certain cases of stone in both kidneys if there is gross destruction of renal tissue with infection on one side and a moderately good kidney with little or no infection on the other.

In operating for bilateral calculi, Winsbury-White elects to operate on the less affected side first. The value of nephrectomy in cases in which stones are present in both kidneys is discussed.

There were 55 cases of ureteral calculus; in 45 involvement was unilateral and uncomplicated by renal calculus; in 1 it was bilateral, whereas in 9, a stone was present either in the corresponding or in the opposite kidney.

There were 2 deaths in Winsbury-White's total series of 162 cases, 1 occurring after pelviolithotomy in a single kidney.

Counseller and Priestley<sup>18</sup> stated that the indications and the type of operation for removal of a single stone that is too large to pass spon-

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18. Counseller, V. S., and Priestley, J. T.: The Present Conception of Renal Lithiasis, *J. A. M. A.* **104**:1309 (April 13) 1935.

taneously have been fairly well standardized. In the past nephrolithotomy was the operation of choice for removal of a renal stone, but, except for a stone or stones situated just beneath the renal capsule or impacted high in one of the calices, pelviolithotomy is now the preferable procedure. This is particularly true in cases of a single stone situated in the renal pelvis. By careful manipulation many single or multiple stones situated in the calices can also be removed through incision of the pelvis of the kidney. Removing stones through the renal pelvis does not destroy important structures; large blood vessels are not divided, and satisfactory anatomic closure can be obtained. Fistulas of the urinary tract rarely follow this procedure. Pelvionephrolithotomy is used to advantage when a stone is impacted in a calix or when there are branches extending into one or more calices.

Conservative operations depend on the type, size and situation of the stones, on the presence or absence of infection, on the status of the opposite kidney, on the involvement—whether bilateral or unilateral—on renal function and on the general condition of the patient. There is still considerable divergence of opinion regarding management of the stag-horn or coraliform type of stone. These are frequently symptomless and are discovered only in the course of routine examination; their removal usually has been difficult and has been attended with some destruction of the parenchyma of the kidney. In the past few years it has been possible to remove successfully stag-horn stones from the kidney in most cases; in several of these cases there were stones in both kidneys; serious injury to the kidney, its pelvis or ureter did not take place, and all fragments were removed. The method employed in removal consisted of retracting the parenchyma to the bifurcation of the calices, thus giving direct access to the calices through a V-shaped incision in the renal pelvis. By nephrectomy over each calix the portion of stone in that calix was removed, the forefinger of each hand being used, one in the pelvis and one in the calix. Bleeding from opening of the parenchyma was controlled by suture or by Pezzar catheters pulled snugly into the calix.

Surgical removal of stones from the kidney is not adequate treatment for renal calculi; the postoperative care and management is an important phase of the treatment. This is particularly so if infection is present in the urinary tract or if a definite tendency toward recurrent calculi has been demonstrated. If renal function is materially interfered with, subsequent attention to these factors is of significance. All calculi and fragments of stone should be completely removed at the time of operation if recurrence is to be prevented. This may be accomplished only by the routine use of fluoroscopic and roentgen examination at the time of operation. Although the influence of obstruction of the kidney in

the formation of stones is not fully understood, every effort should be made to provide free drainage of urine from the upper portion of the urinary tract after removal of stones. Not infrequently, because of obstructing factors such as anomalous vessels, bands of fibrous tissue, acute angulation of the ureter or other causes, obstruction may be discovered at the ureteropelvic juncture. This should be corrected if possible at the time of operation. Complete elimination of infection is important in preventing subsequent formation of calculi. Different aids may be used in removing infection from the urinary tract. If the kidney is extensively injured and is the seat of marked infection at the time of operation, it is frequently advisable to insert a nephrostomy tube, preferably through the lower calix, in order to aid rehabilitation of the kidney. This not only provides excellent drainage but permits direct pelvic lavage as often as desired. Various metabolic disorders may fundamentally be responsible for formation of calculi. Routine chemical analysis of the calculus removed may aid in detecting these disorders. In addition, microscopic examination of the urine may reveal cystinuria or the presence of uric acid crystals.

Sutherland<sup>19</sup> stated that 479 patients operated on at the Mayo Clinic for renal calculi since 1924 have been reexamined by means of the fluoroscope for the presence or absence of remaining stones or particles. The procedure in the majority of cases was to make a fluoroscopic examination of the kidney after all appreciable calculi had been removed. No evidence of persisting shadows was revealed in 409 cases of the series. In 70 cases (14 per cent) fluoroscopic observations disclosed persisting shadows which were localized, and the remaining stones or fragments were searched for and removed. In a few instances repeated observations were necessary to accomplish the task successfully.

For some years at the Mayo Clinic, roentgenograms of the kidney have been made at the time of operation; a cassette holding a 10 by 12 inch (25.40 by 30.48 cm.) film and intensifying screens have been used. The cassette and film are covered with a sterile towel and are held against the side of the patient; the roentgenograms have proved satisfactory. A preliminary observation is made to get the kidney in proper perspective, and a roentgenogram is made and then sent for immediate development. If a shadow is visible it can be localized in subsequent observations, and usually by the time the surgeon has found and removed the calculus or fragment, the finished roentgenogram is available for checking with the surgical findings. Corroboration of the fluoroscopic findings when they are negative or elucidation of shadows not seen by the physician who makes the fluoroscopic examination is hastened by

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19. Sutherland, C. G.: Renal Roentgenoscopy and Roentgenography at the Operating Table, *J. Urol.* **33**:1 (Jan.) 1935.

this procedure, and the information is made available to the surgeon without undue delay.

The apparatus used for making fluoroscopic observations of the kidney at the operating table is essentially the bedside unit used in the majority of hospitals. It consists of a transformer and autotransformer enclosed in a metal cabinet and mounted on large casters for portability. The cabinet is attached to a tube stand with a horizontal arm having universal joints for supporting the tube. The tube is of the Coolidge radiator, self-rectifying type, mounted in a lead glass shield. The ordinary cone is replaced by one 30 cm. in length, with a diameter of 6 cm. at its proximal end and 8 cm. at its distal end. This cone converges the rays on the kidney, and its length allows the unit to be brought closer to the patient without menace to safety.

Herman and Lee<sup>20</sup> stated that lithiasis due to cystine is predominantly a disorder of males. Cystinuria, as has long been known, is an inheritable condition characterized by an essential fault in protein metabolism leading to incomplete oxidation of sulphur. Accordingly, cystine, a sulphur-bearing amino acid, is formed in an amount too great to be excreted chiefly by the kidneys. The condition lacks surgical interest as long as cystine is held in solution, but crystallization is prone to occur, with lithiasis as a frequent result. Lithiasis due to cystine is found in isolated segments of the urinary tract, and nephrolithiasis due to cystine is no more frequently bilateral than are other varieties of nephrolithiasis. Undoubtedly, localization in formation of stone is usually dependent on local factors, but cystine stones may form in the kidney in the absence of infection or demonstrable mechanical defect. Multiplicity of stones and their rapid development are likewise suggestive of lithiasis due to cystine although it is not highly characteristic of cystine calculi in the kidney to grow to enormous proportions, as some authors claim. Data on lithiasis due to cystine, as obtained from roentgen examination, lead to the conclusion that the texture of the stones, as well as the atomic weight of their constituents, determines their radio-opacity. The treatment of urolithiasis due to cystine is the same in principle as that applied in cases of other varieties of urinary stone. However, a more conservative attitude should be assumed toward operative treatment in the case of nephrolithiasis due to cystine for the following reasons: 1. Large cystine stones will pass more readily than large stones of other varieties. 2. There is a marked tendency to rapid recurrence of the condition in the absence of proper postoperative treatment and, some writers claim, in spite of it. 3. In some instances cystine stones may be dissolved. Cystine is soluble in an alkaline medium; this fact rationalizes the admin-

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20. Herman, Leon, and Lee, W. E.: Cystine Nephrolithiasis, *Ann. Surg.* **101**: 746 (Feb.) 1935.



istration of sodium bicarbonate, ammonium carbonate and similar drugs in the attempt to dissolve stones or to prevent their reformation. The only function of alkalis in prophylaxis is to maintain the solubility of cystine in the urine; this substance in cystinuric patients is constantly present in excessive amount, and a strong tendency to crystallization exists. Dietary regulation is based somewhat on empirical grounds, although the rate of excretion of cystine is in direct ratio to the protein content of the diet. The limitation, if not the exclusion, of proteins from the diet, particularly of those rich in sulphur, is a rational phase of prophylactic treatment.

*Surgical Technic.*—Colston <sup>21</sup> stated that the term “complete nephro-ureterectomy” should be used to describe only the operation in which complete excision of the upper part of the urinary tract, including the intramural portion of the ureter, has been performed. A simplified technic has been described, by which complete nephro-ureterectomy can be accomplished, avoiding the technical difficulties and postoperative complications which may occur when a cuff of mucous membrane about the orifice of the ureter is excised. After sectioning the ureter above the bladder Colston removes the clamp on the bladder side of the ureter, and the lumen of the stump of the ureter is completely destroyed by a fulgurating electrode. In many cases of renal tuberculosis, in addition to nephrectomy there is also a definite indication for ureterectomy. Although a superficial tuberculous invasion of the ureter will heal spontaneously when the diseased kidney above it has been removed, there are certain cases of extensive, deep-seated ureteritis which must be responsible for the occasional infections of the wound which are seen and for sinuses which may persist after simple nephrectomy. The extent of the tuberculous process in the ureter can best be determined by study of the ureterogram. Alternate regions of constriction and dilatation, with a moth-eaten appearance of the edges of the pyelographic medium in the ureter, indicate extensive ulcerative tuberculous ureteritis. In such cases excision of the ureter is necessary. The operation of nephro-ureterectomy, or ureteronephrectomy, is easily performed from a technical standpoint and entails little more shock to the patient than simple nephrectomy.

Despite the fact that the tendency in renal surgery is toward conservatism, resection of the kidney is performed relatively infrequently.

The resections are of two types: (1) resection of normally formed kidneys, and (2) resection of half of a double kidney.

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21. Colston, J. A. C.: Complete Nephro-Ureterectomy: A New Method Employing the Principle of Electrocoagulation to the Intramural Portion of the Ureter, *J. Urol.* **33**:110 (Feb.) 1935.

Kretschmer<sup>22</sup> reported ten resections of the first type and six of the latter. As a rule, the operation is performed more frequently on double kidneys, usually for hydronephrosis and infection, with or without stones. It may become an operation of necessity on solitary kidneys, in cases of circumscribed collections of stones, especially with infection, of stones in a calix, with dilatation and with strictures of the neck and of encysted stones with formation of abscess or carbuncle. It may be an operation of choice when these conditions are present in one of two kidneys. Additional indications are encountered in the following instances: (1) in cases of stone in both kidneys in which one pole is diseased or in cases in which there exists a circumscribed stone with formation of pus; (2) in cases of partial hydronephrosis of the upper or lower pole, with formation of stone; (3) in cases of solitary cyst of the kidney, in which group resection is at present recognized as the operation of choice and, as a rule, is simple and easy of execution; (4) in cases of double kidney with double pelvis, in which one-half gives evidence of the presence of hydronephrosis, severe infection or stone.

In Kretschmer's series hemorrhage was not troublesome either at the time of operation or subsequently.

In the cases of double kidney, the vascular supply to the diseased half was ligated before the resection was performed, and the operation was practically bloodless. In normally formed kidneys there was no difficulty in controlling the bleeding with sutures.

Postoperative fistula did not occur. It can be prevented by careful suturing of the opened calices and parenchyma.

*Tuberculosis.*—Woodruff and Bumpus<sup>23</sup> stated that there is sufficient laboratory, as well as clinical, evidence that tuberculous infection of the kidney actually heals. Healing, however, does not prohibit reinfection. There should be adequate hygienic treatment of renal tuberculosis in its early stage, preferably in a sanatorium. Nephrectomy should be performed only when evidence of extension of the disease exists, when caseocavernous conditions can be demonstrated, or when, on test, it is evident that renal function has become markedly diminished.

Greenberger, Wershub and Auerbach<sup>24</sup> reported that of 500 cases of tuberculosis in which necropsy was performed, in 252 evidence of tuberculous infection of the kidney was found. Miliary tubercles that

22. Kretschmer, H. L.: Resection of the Kidney, Surg., Gynec. & Obst. **60**: 984 (May) 1935.

23. Woodruff, S. R., and Bumpus, H. C., Jr.: Is Nephrectomy Always Indicated Following a Diagnosis of Unilateral Renal Tuberculosis? J. A. M. A. **104**: 716 (March 2) 1935.

24. Greenberger, M. E.; Wershub, L. P., and Auerbach, Oscar: The Incidence of Renal Tuberculosis in Five Hundred Autopsies for Pulmonary and Extrapulmonary Tuberculosis, J. A. M. A. **104**:726 (March 2) 1935.

could be recognized grossly were found in 228 cases (45.6 per cent). In this group the involvement was found to be bilateral in 187 cases (82 per cent) and unilateral in 41 cases (18 per cent). The youngest patient of this series was 9 months old, and the oldest, 74 years; the average age was 36. In the group were 157 male and 71 female patients; there were 154 patients belonging to the white, 72 to the Negro and 2 to the yellow race. Only 25 per cent of the patients had urinary symptoms. The most common complaints were nocturia and frequency.

Of the total number of cases in which necropsy was performed, "organ tuberculosis," that is, destruction of the renal substance, was found in only 24 cases (4.8 per cent). In this group the involvement was found to be bilateral in 13 cases (54 per cent) and unilateral in 11 cases (46 per cent). The youngest patient was 23 and the oldest 59 years of age; the average age was 39. There were 20 men and 4 women; 21 white patients and 3 Negroes. In 60 per cent of the cases in this classification there was some evidence of urinary disturbances; these were mild as compared to the pathologic changes found at post-mortem examination.

In 16 cases the tuberculosis was extrapulmonary and the renal involvement bilateral. In all but 1 case the disease was of the miliary type. The youngest patient of this group was 1½, and the oldest 56 years of age; the average age was 22. The cause of death was tuberculous meningitis in 10 cases, tuberculous peritonitis in 4 cases and generalized miliary tuberculosis in 2 cases. Organ tuberculosis is the pathologic condition most frequently encountered by the clinician and urologist. It is the type of lesion that produces definite changes as revealed by pyelograms and is clinically recognizable.

Young,<sup>25</sup> in discussing a paper read before the Section on Urology of the American Medical Association, stated that the subject of urogenital tuberculosis is of such importance that thorough consideration should be given to it before presenting to the medical world the statement that the Section on Urology even contemplates the advisability of not performing nephrectomy in the presence of an early tuberculous lesion on one side. The diagnosis of this disease is difficult. Tubercle bacilli are not always to be found in the urine, and guinea-pigs do not always die after receiving injections of urine from a patient who has definite renal tuberculosis. After a careful recent study of all his cases of tuberculosis of the genito-urinary tract Young is convinced not only that early nephrectomy and partial ureterectomy are desirable but that whenever tuberculosis has involved an epididymis it is practically certain that the vasa deferentia, seminal vesicles and prostate gland are also involved, in which case bilateral radical operation on the seminal tract is indicated as soon as the patient has recovered from the nephrectomy.

25. Young, H. H., in discussion on Woodruff and Bumpus.<sup>23</sup>

LeComte<sup>26</sup> stated that definite distinction should be made between healing of a lesion of renal tuberculosis and cure of the disease in the entire organ. Some evidence of healing may be found in practically every tuberculous kidney, but the occurrence of a complete cure may be questioned. To regard a cure as established in a surgical form it would be necessary to show that the previously diseased kidney was capable of secreting a urine free from pus and bacilli and was free from evidence of the disease both on urography and on other roentgen study. LeComte deplored the tendency to discontinue the use of operation in cases of early unilateral tuberculosis of the kidney; it is in these instances that the best results are obtained.

Eisendrath<sup>27</sup> stated that renal tuberculosis and true calculus are associated in approximately 1.8 per cent of all cases of renal tuberculosis. He tabulated 40 cases, reported since 1920, the majority of which were instances of formation of true calculi in tuberculous kidneys; 5 of these cases were personally observed. The cases are divided into four clinical groups, the first two of which are of especial importance. In the first group, if the concomitant tuberculosis in a case of calculus of the kidney or ureter is overlooked, there is danger of formation of a persistent postoperative fistula as well as of early recurrence of calculi. Five cases reported since 1920 of calculous anuria following nephrectomy for tuberculosis at intervals of from twenty-six days to one year are cited. A number of similar cases were reported before 1920 by Eliot, Kuemmell and others. The making of plain roentgenograms even in cases of well marked renal tuberculosis should be considered a routine measure in order to detect the presence of renal or ureteral calculi.

Gibson<sup>28</sup> stated that the common definition of autonephrectomy is "a stricture of the ureter which completely closes the lumen so that no secretion reaches the bladder." This definition does not give the true meaning of the word. Autonephrectomy should be said to have taken place in cases of renal tuberculosis in which there is not only complete closure of the ureter, with cessation of all symptoms, but also complete destruction and transformation of the kidney into a quiescent, shrunken caseosclerotic mass, so that surgical removal is unnecessary.

Two cases of autonephrectomy are reported. One is unusual in that complete calcification of the kidney and ureter occurred and that tuberculosis of the urinary tract had existed for thirty-five years. Approximately 0.5 per cent of tuberculous kidneys undergo complete calcification. With quiescent total calcification coincident with a normal bladder, the

26. LeComte, R. M., in discussion on Woodruff and Bumpus.<sup>23</sup>

27. Eisendrath, D. N.: Renal Tuberculosis and Nephrolithiasis as Associated Diseases, Surg., Gynec. & Obst. **60:77** (Jan.) 1935.

28. Gibson, T. E.: Nephrectomy Versus Autonephrectomy in Renal Tuberculosis, J. Urol. **33:145** (Feb.) 1935.

prognosis appears to be equally favorable whether the patient is treated medically or surgically. In the problem of nephrectomy versus autonephrectomy the conclusion seems justified that in certain cases of unilateral renal tuberculosis, conforming to the definition of autonephrectomy suggested by Gibson, nephrectomy is not necessary, or at least the risk of noninterference is no greater than the risk of nephrectomy.

*Hydronephrosis.*—Ragnotti<sup>29</sup> undertook researches in which he subjected the ureters to mechanical or chemical denervation in order to discover whether the genesis of the so-called "dynamic hydronephrosis" lies in pure and simple lesions of nerve tissue, or whether, and to what extent, anatomic factors also play a rôle in its production. Comparing the histologic observations on the treated ureters with their functional behavior and with the lesions presented by the kidneys he concluded that when the denervation is brought about by chemical means (isophenol) the simple change of innervation induces nothing more than transitory modifications of ureteral motility, almost exclusively affecting the peristaltic and not the pendular movements, and does not go so far as to provoke permanent and progressive anatomic lesions and, still less, hydro-ureteronephrosis, since the changes never get beyond the phase of reversibility and tend to disappear on regeneration of the intrinsic nervous system.

But when the lesion of the innervation results also in modification of the histologic structure of the ureter, as usually occurs when denervation is brought about by mechanical means (adventitiectomy, decortication of the ureter) producing sclerotic changes in the organ, the diminution of motility is more pronounced; to this is added alteration of the normal elasticity and distensibility of the ureteral wall, since there is constant formation of a periureteral connective tissue which at the periphery causes adhesions and centrally has a tendency to infiltrate, disorganize and replace the muscle fibers, until in advanced cases there occurs a true replacement of connective tissue of the tunica muscularis capable of profoundly changing the kinetics of the ureter. This interruption of the continuity of the muscular tunic must produce far graver consequences than simple destruction of the rete nervosa. For the process of sclerotization of the muscular tunic not only results in functional disturbances through changes of the normal elasticity and distensibility of the ureteral wall, tending to obstruct the normal outflow, but may also be the cause of a true mechanical obstacle when it produces cicatricial stenosis, angulation and kinking of the ureter. But not even

29. Ragnotti, Ercole: Considerazioni e ricerche sul significato patologico e sulla produzione sperimentale della "idronefrosi dinamica": Conseguenze anatomiche e funzionali della enervazione periureterale, Arch. ital. di chir. 38:367 (Nov.) 1934.

in these cases does atony (inertia) supervene (unless indeed the sclerosis is total), but rather dyskinesia of the entire ureter occurs. The existence, however, of automatic movements does not preserve the kidney from the appearance of graver lesions, since these movements are no longer endowed with expulsive activity.

Mechanical denervation has as its result, therefore, a hydronephrosis which, lacking the causal factor of stenosis, must with good reason be regarded as attributable to injury to function or in other words as "dynamic." The basis of this "dynamic hydronephrosis" is, however, anatomic in a strict sense, that is, it is connected with anatomopathologic changes of the wall of the ureter and is not the pure and simple result of the lesion of nerve tissue.

Kimbrough<sup>30</sup> stated that the conservative treatment of hydronephrosis is essential in cases in which etiologic factors are bilateral. Satisfactory results have been obtained by plastic surgery in cases in which the hydronephrotic sacs have been large, in those in which there has been stricture at the ureteropelvic juncture, in cases of anomalous renal position and in cases in which obstruction has been caused by large, aberrant vessels. Complete relief from clinical symptoms is not always obtained, but the moderate morbidity resulting in some cases is compatible with a comfortable existence and is only a small handicap to gainful occupations. The type of operation must be selected to meet the requirements in each individual case. The following points are important in the surgical treatment of hydronephrosis: drainage by nephrectomy, splinting by ureteral catheter, adequate perirenal drainage, fixation of the kidney in proper position, renal sympathectomy to improve circulation and prevent postoperative pain, avoidance of division of large aberrant vessels and correction of deformity of the proximal portion of the ureter.

*Trauma.*—Mauro<sup>31</sup> discussed the means of diagnosis in cases of ruptured kidney in which the fact of trauma has been concealed from the surgeon, as in a case recently observed by him. The mechanics of this rupture was one that he has not found in the literature: A fall flat on the abdomen caused a large, coraliform calculus to puncture with its point the renal artery at its entrance to the pelvis, and a grave retroperitoneal hemorrhage resulted. The enlarged kidney, which was ptotic, had been pushed against the spinal column by the blow, at the transverse processes of the second and third lumbar vertebrae; the wall of the

30. Kimbrough, J. C.: Surgical Treatment of Hydronephrosis. *J. Urol.* **33**:97 (Feb.) 1935.

31. Mauro, Mario: Su di un nuovo meccanismo di rottura del rene: Contributo allo studio della sindrome acuta emorragica retroperitoneale. *Ann. ital. di chir.* **13**:819 (July 31) 1934.

renal pelvis and the hilus had been pushed out of place and injured between the stone and the bony resistance of the spine. The breach in the pelvis had remained plugged by the calculus, and it was the lesion of the artery that caused the rapid hemorrhage into the retroperitoneal space. The slightness of the hematuria in this case was deceptive; it was followed by anuria either from reflex action or from renal blockade.

In cases of this kind the retroperitoneal syndrome caused by the rapid hemorrhage into the perirenal cellular tissue is characteristic. The toxic symptoms that arise give Mauro the impression that there is rapid and marked absorption of substances formed as the result of undeniable changes of the blood that has escaped, possibly an intoxication of the vegetative nervous system through absorption of protein substances produced by changes in the extravasated blood.

When the fact of trauma has been concealed, as in this case, diagnosis is difficult, especially if renal signs are not evident and if the perirenal hematoma is not readily perceptible, owing to excessive abdominal rigidity and absence of fulness in the lumbar region. One thinks rather of rupture of the liver or spleen to explain the anemia and the peritoneal reaction, or of intestinal occlusion—a diagnosis that is often made. The presence of a concomitant abdominal lesion, of course, leads to confusion and aggravates the symptoms.

Lancinating pain, frequently syncopal in its effects, is always present at the start, just as it is in cases of ruptured extra-uterine pregnancy. The pain is often accompanied by shock and loss of consciousness, and even by collapse; the temperature may be elevated from rapid absorption of blood, or lowered from shock. The lumbar region is usually sensitive and contracted, the abdomen is meteoric and pain is elicited on pressure. Rigidity is a characteristic sign; it may hinder good palpation and make it impossible to discover the perirenal hematoma.

In Mauro's case the blood was diffused in the surrounding subperitoneal connective tissue down to the crest of the ilium and had widely detached the peritoneum toward the median line. Nephrectomy was inevitable, not only for hemorrhage but also on account of the precarious condition of the organ.

Abeshouse<sup>32</sup> stated that rupture of the pelvis of the kidney proper is a relatively rare condition; it may be of the traumatic or of the spontaneous type. Rupture of the pelvis of traumatic type may occur in a congenitally normal kidney or in a kidney that is the site of acquired inflammation or obstruction. The rupture is usually the result of direct or indirect trauma exerted against the kidney. The spontaneous type of pelvic rupture usually occurs in a kidney which is the seat of a chronic

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32. Abeshouse, B. S.: Rupture of the Kidney Pelvis: Review of the Literature, *Surg., Gynec. & Obst.* 60:710 (March) 1935.

pyelonephritic process or of which the pelvis is dilated as the result of obstruction of the ureter or of the pelvis. Rupture of a pathologically weakened pelvis may also occur as the result of instrumental perforation, or it may follow the exertion of increased pressure in the syringe method of pyelography. In rare instances perforation may be attributable to chemical necrosis following injection, by mistake, of a strong alkali in the course of pyelographic studies or renal lavage.

The traumatic type of rupture has a greater incidence than the spontaneous type. The former apparently occurs more frequently among males than among females. The spontaneous type occurs with about equal frequency in both sexes. There is no definite complex of symptoms or clinical syndrome that is absolutely typical or constantly associated with rupture of the pelvis of a kidney. The presence of the lesion should be suspected if there is an antecedent history of chronic pyelonephritis or hydronephrosis secondary to calculus in the pelvis or ureter and if there is a sudden, sharp pain in the renal region followed by sudden or gradual swelling or the appearance of a mass in the same region, accompanied by chills, fever, nausea, vomiting and—frequently—shock or collapse. The clinical impression that the pelvis is ruptured should be confirmed by urologic study, including pyelography, which is the only dependable method of diagnosis.

Successful treatment in cases of ruptured pelvis is directly dependent on early diagnosis and immediate surgical intervention, which may be either conservative or radical. The conservative procedure includes incision and drainage and, if possible, correction of pathologic processes responsible for rupture and repair of the pelvic laceration. The radical procedure is nephrectomy, provided the opposite kidney is healthy. In the case of toxic and debilitated patients treatment should be in two stages: preliminary incision and drainage followed by nephrectomy or conservative repair at a later date.

*Cysts.*—Quinby and Bright<sup>33</sup> stated that there are three varieties of large, single cysts of the kidney: The first is the simple, thin-walled cyst containing a serous fluid. This type of cyst, although formed of the parenchyma of the kidney, bears no anatomic, causal relation either to the pelvis or to a calix. Of the second variety are cysts which, although they compress and push aside the secretory tissue of the kidney in the same way as do cysts of the first type, have a deeper origin and communicate with some portion of the renal pelvis by a minute channel; these are designated as pyelogenic cysts by some writers. A third variety includes cysts which lie outside the kidney proper, communicating

33. Quinby, W. C., and Bright, E. F.: Solitary Renal Cysts: Their Symptoms When Situated at the Upper Pole of the Right Kidney, *J. Urol.* **33**:201 (March) 1935.



with the pelvis but not representing a true dilatation of it as does the pyelectasis associated with hydronephrosis. These form the so-called parapelvic type of cysts. There is also described a fourth variety, the hemorrhagic solitary cyst, the name being derived from the content of the cyst.

An analysis of the symptoms associated with these cysts of the upper pole of the right kidney has been made from 32 cases, reports of which have been found in the literature, together with the 4 instances reported by Quinby and Bright. More than 50 per cent of the patients had pain in the right upper quadrant of the abdomen, under the costal margin. This pain usually did not radiate. A few patients complained only of discomfort in that region. One fourth of the patients had pain in the right side of the back. The pain extended anteriorly in a few of these cases, and sometimes it extended down the course of the ureter. In one third of the cases there were symptoms of cystitis, and in one third also chills and fever were reported. In two thirds of the group neither the kidney nor any tumor could be felt. When the cyst was palpable it usually was so abdominally, not bimanually. Only a few patients complained of tenderness on palpation. In about two thirds of the cases, therefore, physical examination gave entirely negative results. Pyelography in the 8 cases in which it was performed gave the most accurate diagnosis, disclosing deformity or displacement of the upper calices in 75 per cent of the cases. In reviewing a large number of cases of solitary cyst of the kidney situated at other sites than the upper pole of the right kidney it was found that there were 41 cases in which pyelography was recorded; in 34 (83 per cent) of these cases pyelograms showed abnormal conditions. Accurate preoperative diagnosis of cysts of the upper pole of the right kidney has rarely been made. Only in 1 of Quinby and Bright's 4 cases and in 5 of 30 reported instances was a correct diagnosis made.

*Ptoxis*.—Spurr<sup>34</sup> undertook to prove by experimentation that weakness of the abdominal wall and diminution of intra-abdominal pressure do not play the important rôle that currently has been assigned to them in the production of movable kidney. As a result of his studies he was convinced that in a great number of cases nephroptosis is only the most important symptom of a general dyscrasia, as has repeatedly been asserted by Pende, Stiller, Tuffier and others, and is accompanied, among other things, by splanchnoptosis, the nature of which should be understood. Without undertaking to resurrect the old theory of Glonard, that enteroptosis is the chief cause of renal displacement, or the anatomic theories of Longyear, it cannot be denied that if one always checked

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34. Spurr, Ricardo: Nefroptosis y esplanchnoptosis, *Rev. méd. latino-am.* 20:1 (Oct.) 1934.

up the state of the abdominal viscera in cases of movable kidney one would cease to be surprised by the discovery that the stomach, duodenum, liver and colon suffer an appreciable, and in some cases, a considerable displacement, explaining the digestive symptoms observed in patients with movable kidney. All authors who have given attention to splanchnoptosis, and especially to gastropptosis, have confirmed the theory that displacements of the digestive tube are always accompanied by displacement of the right kidney or of both kidneys. This is explained by the intimate anatomic relation of the right kidney with the second portion of the duodenum, with the ascending and transverse colon and with the liver, as well as by that of the left kidney with the transverse and descending colon. Since 1922 Spurr has systematically carried out examination of the digestive apparatus of patients with movable kidney and has found in all of them a marked splanchnoptosis, as the roentgenograms accompanying his article show. The existence of nephropptosis and splanchnoptosis, as associated lesions in young patients presenting symptoms of the "vagotonic type of Pende," or the "asthenic habitus of Stiller," seemed to Spurr a sufficient justification for reaffirming the foregoing concept of their etiopathogenesis and for basing his treatment on this premise.

Spurr has found that the surgical fixation of all the organs involved in this combined splanchnoptosis and nephropptosis has always been followed by frank improvement of digestive symptoms, particularly of gastric disturbances, as well as of renal troubles. The operative method which he proposes, and which he has used with good results in 31 cases, he has named cologastrohepatopexy; it comprises five stages, as follows: (1) right rectus incision, 12 inches (30.5 cm. long); (2) appendectomy; (3) exteriorization of the stomach and colon, which are held by Chaput's forceps and an anterior bandlet; (4) fixation of the colon to the anterior aspect of the stomach, with folding "à besace" of the gastrocolic epiploon, and (5) shortening of whatever ligament is at fault. Whenever third degree nephropptosis is present or the patient has symptoms of uronephrotic retention, or renal colic, nephropexy naturally should be performed; this can best be accomplished at the time of the second of the five stages, if renal accidents dominate the clinical picture. However, a patient with a movable kidney should be treated by nephropexy even if the condition has not provoked any acute renal symptoms, in order to prevent complications that might arise later.

Spurr observed that the usual procedures for fixing ptosed viscera to the abdominal wall have the disadvantage of changing the intra-abdominal status and of contracting visceral adhesions that may cause functional disturbances, if indeed the graver complications of volvulus and occlusion by bands do not occur. Impressed by the methods of Beyea and Bier, he believed and demonstrated that he could satisfactorily correct

splanchnoptosis by shortening the great omentum in its gastrocolic portion and fixing the transverse colon to the anterior wall of the stomach; the latter in turn is lifted to a good position by shortening of the gastrohepatic omentum, and the liver is lifted by shortening of the falciform ligament. This method obviates the disadvantages inherent in the type of right nephropexy carried out in Argentina by Alberto Gutierrez, who closes the renal fossa on its lower side and fixes the right colic angle to the upper pole of the kidney (divested of its serosa) and to the parietal peritoneum, a method that results in changes of the intra-abdominal status. No disturbances of the digestive apparatus have resulted in any case in which Spurr has used his cologastrohepatopexy, with or without nephropexy, according to the conditions present, and the intra-abdominal status has suffered no detrimental change.

*(To be concluded)*

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